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AUGUST 1956

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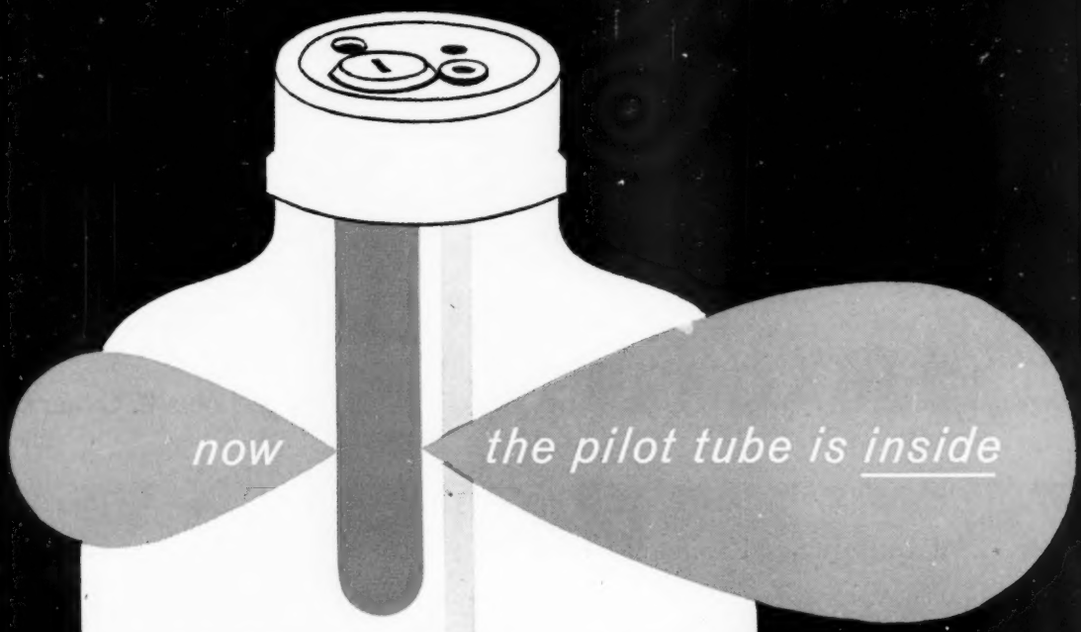

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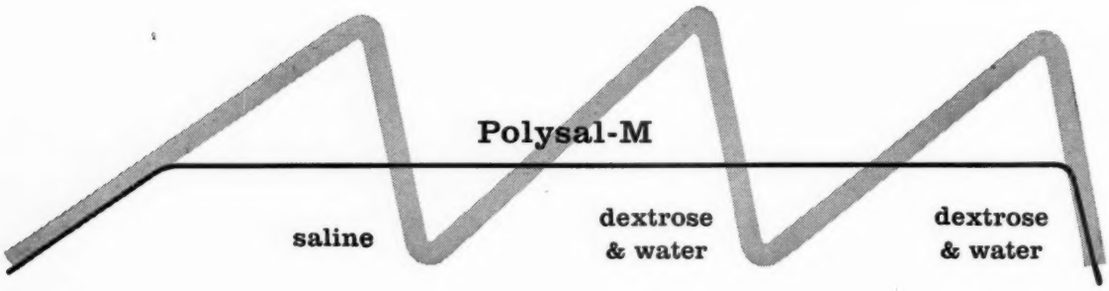

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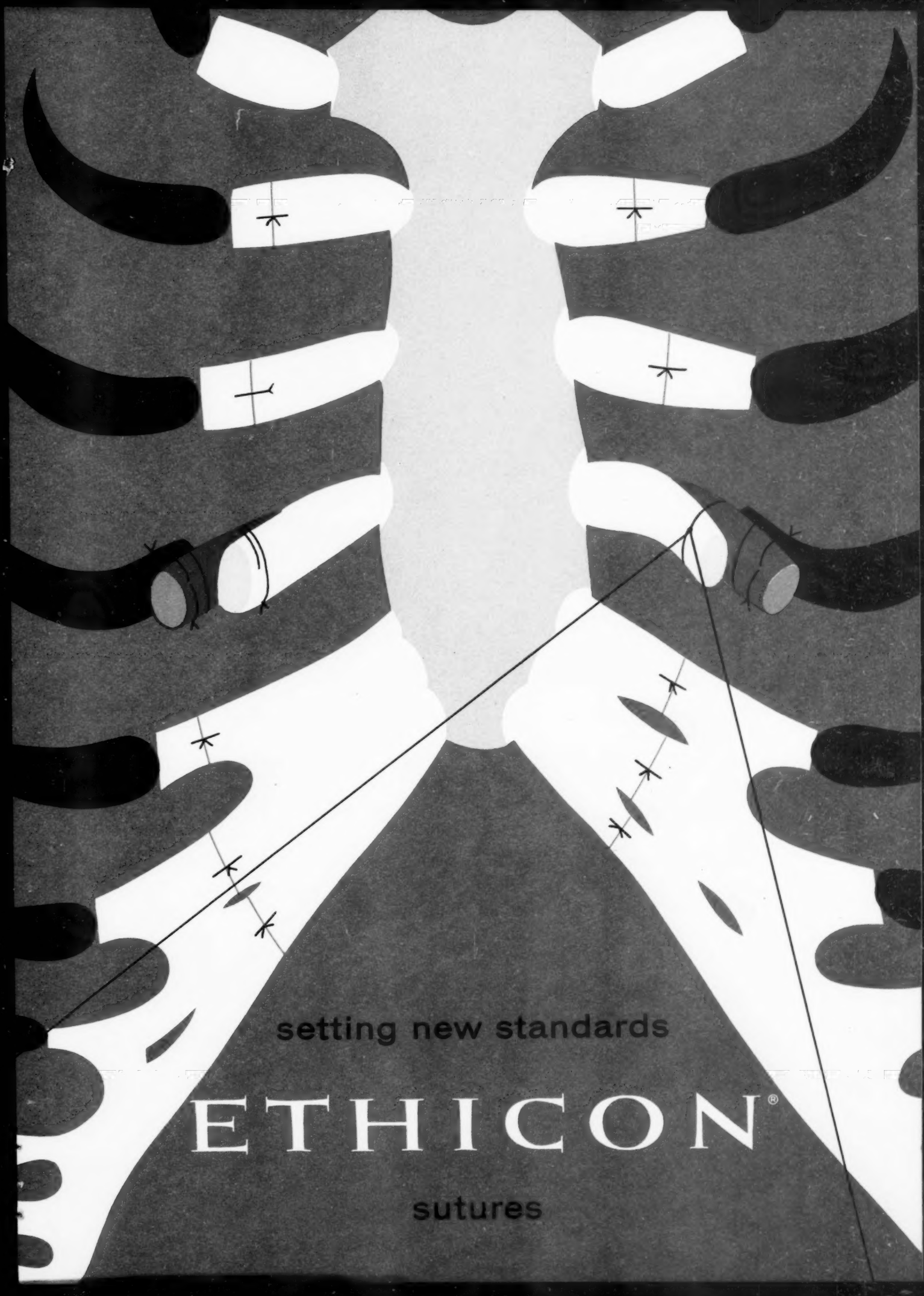
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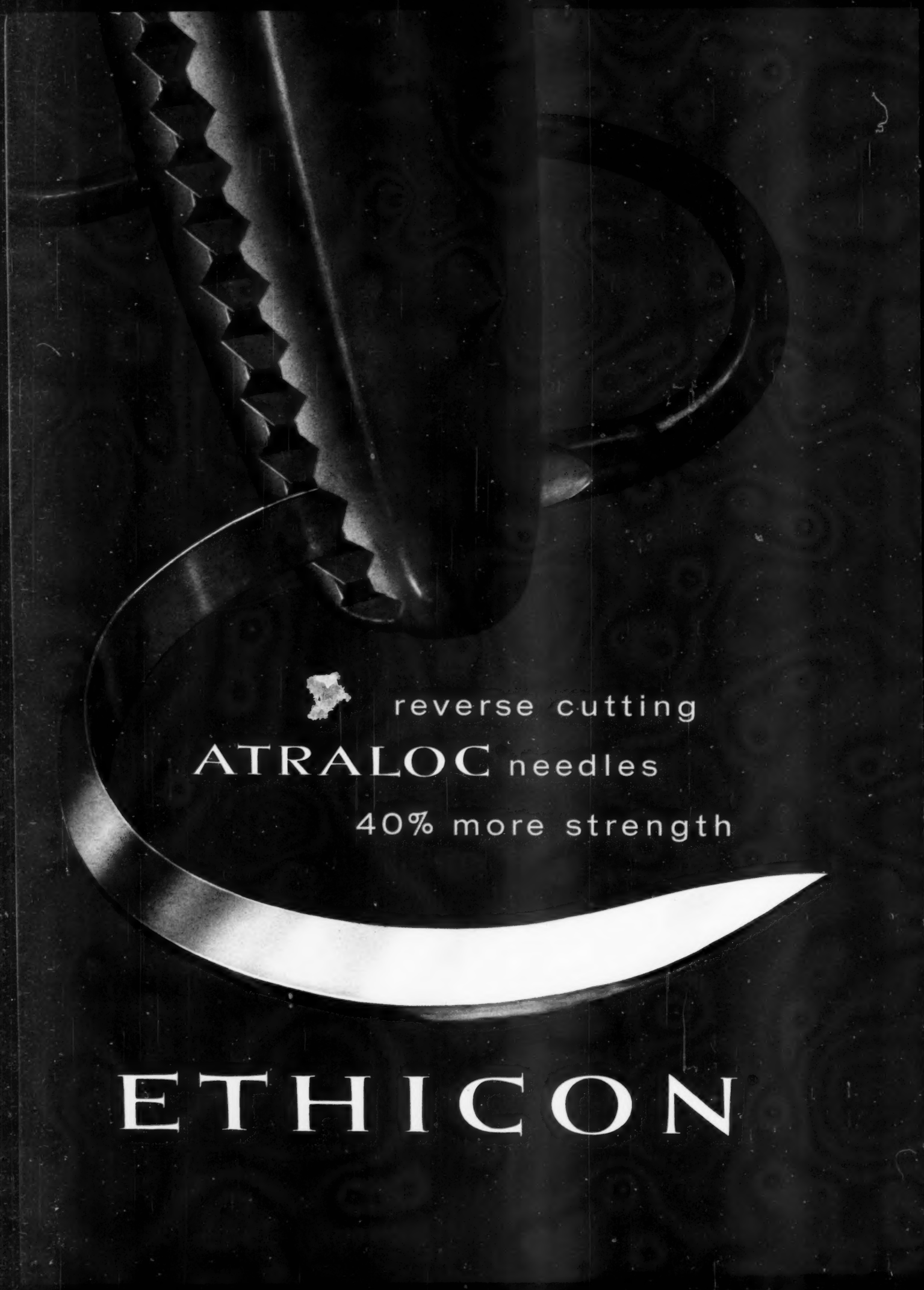
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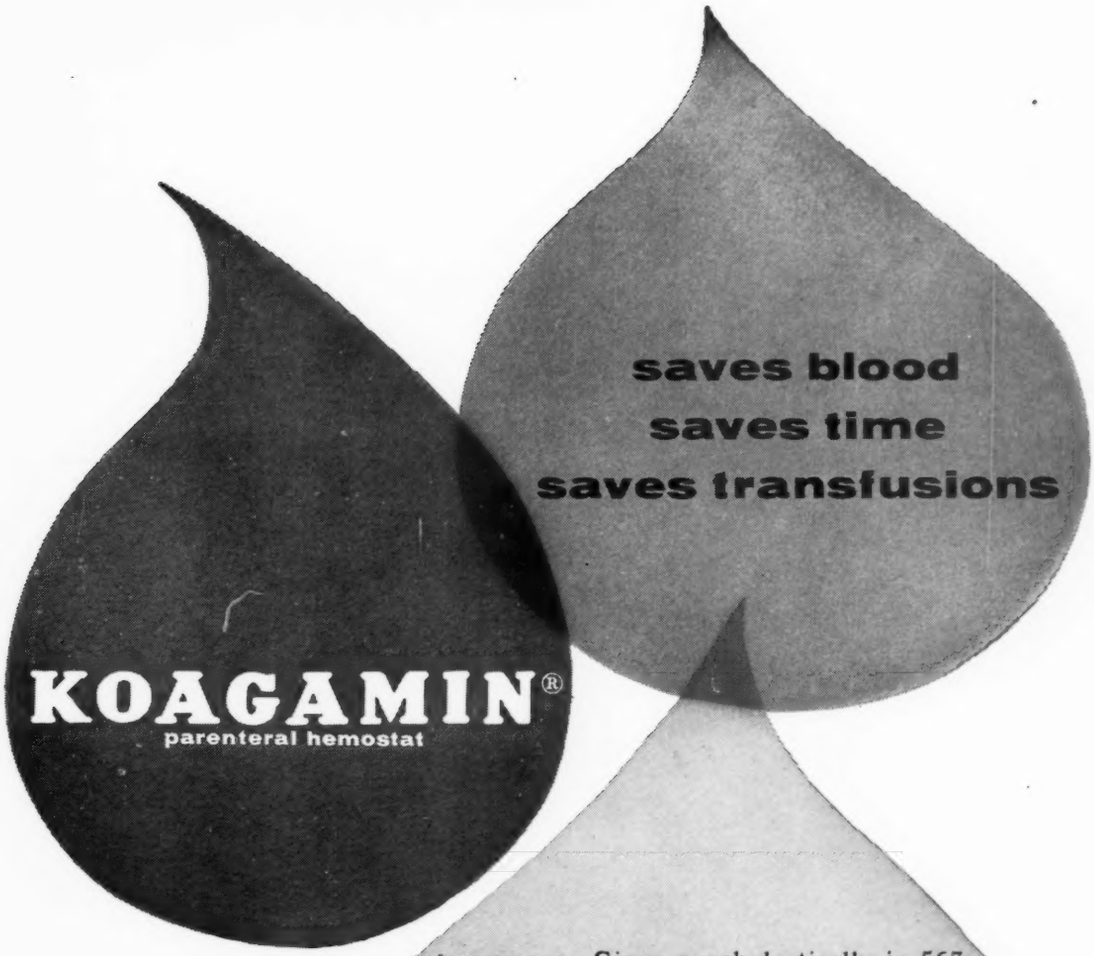

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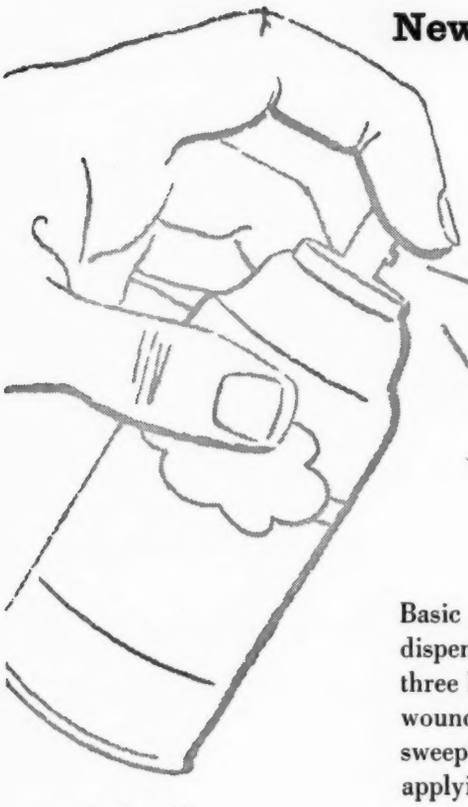

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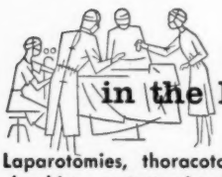

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2. Choy, D.S.J.: A.M.A. Arch. Surg. 68:33 (Jan.) 1954.
3. Rigler, S. P., and Adams, W. E.: Surgery 36:792 (Oct.) 1954.
4. Wexler, D. J., Bromberg, F., Rakieten, M. L., and Ryan, B. J.: Am. J. Surg. In Press.

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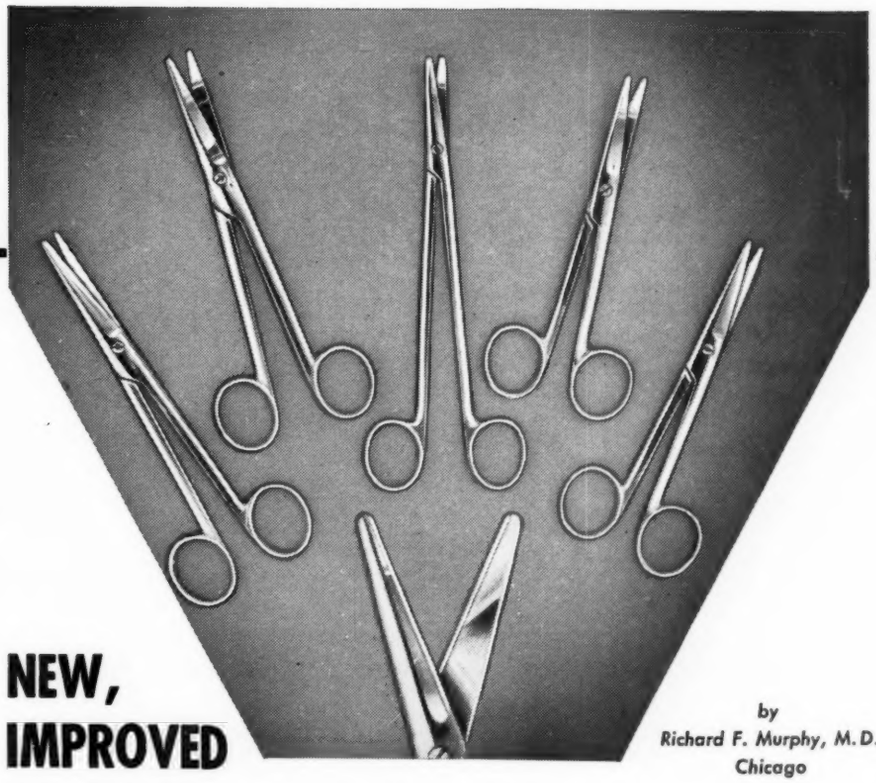

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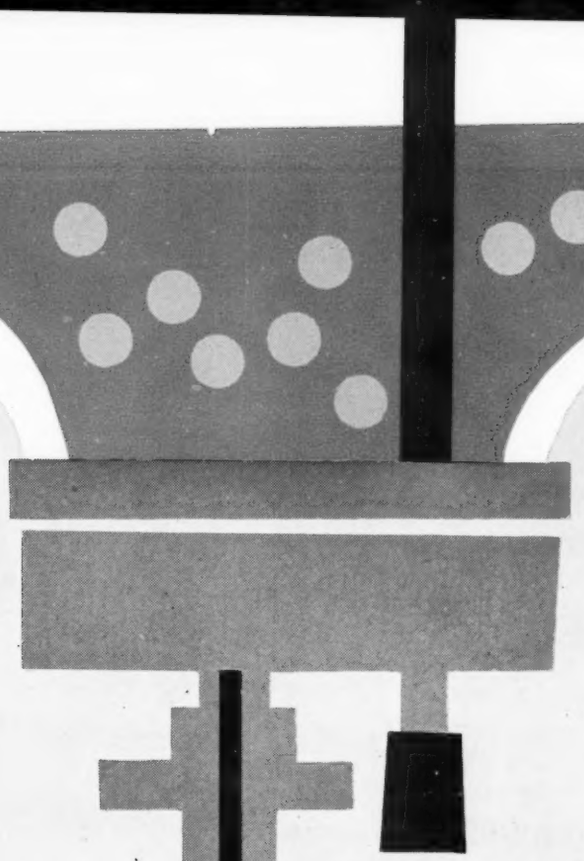

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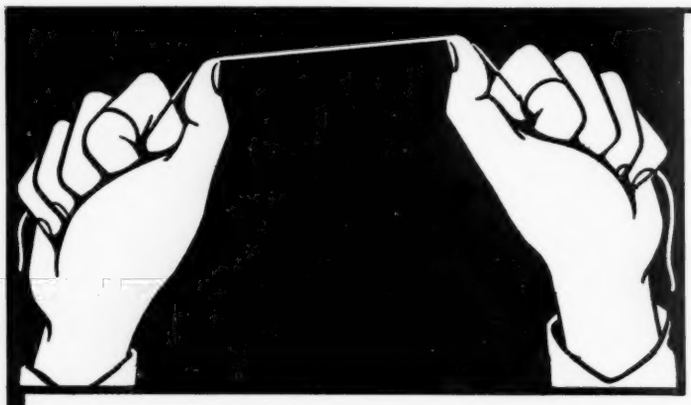

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1. Johnston, T. G., and Cazort, A. G.: J. Allergy 27:90, 1956. 2. Schwartz, E.: New York J. Med. 56:570, 1956. 3. Schiller, I. W., et al.: J. Allergy 27:96, 1956.

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The author emphasizes the need for dependable chemical control of bleeding and oozing, and reviews the methods that have been tried to attain hemostasis, including the use of vitamin K and bioflavonoids.

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He reviews 1051 cases from the files of St. Anthony Hospital, Louisville, Kentucky, of which 330 were treated with Adrenosem Salicylate. 317 were surgical cases and 13 obstetric-gynecological conditions. The treatment was given for symptomatic relief, and as a clinical recourse for patient safety.

In 1015 tonsillectomy patients the following results were noted: There was bleeding in 85 (19.8%) of 429 patients who received no medication. Patients who received a compound of oxalic and malonic acids numbered 115. Of these 16 (14%), developed bleeding. Of 248 patients receiving vitamin K preparations, 47 (19%) had postoperative hemorrhage. 233 patients received Adrenosem Salicylate. Of this group, only 16 (7%) had bleeding.

In other surgical conditions, Adrenosem was used successfully in gastrointestinal bleeding, cataract extraction, incisional seepage, and transurethral prostatectomy. It was also effective in 12 cases of epistaxis.

In the field of obstetrics and gynecology, Adrenosem controlled bleeding in menometrorrhagia, hymeneal laceration, cervical ooze, antepartum and postpartum bleeding, threatened abortion, and in two cases of surgery during pregnancy.

The author points out that in pregnancy, seepage bleeding occurs more because of capillary permeability, and in spite of increased coagulability. Here, Adrenosem becomes specific for strengthening capillary resistance.

Many of the observations in this study, however, involved bleeding incident to trauma of incision, retraction, dissection, tearing and stretching. In these conditions, he reasons that Adrenosem causes hemostasis by its effect on the capillary intercellular cement substance so that the cells draw closer together, and the ends of the capillaries constrict, causing a "self-clamping" mechanism.

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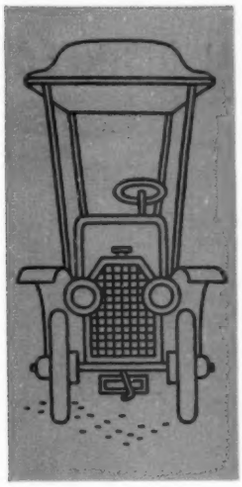

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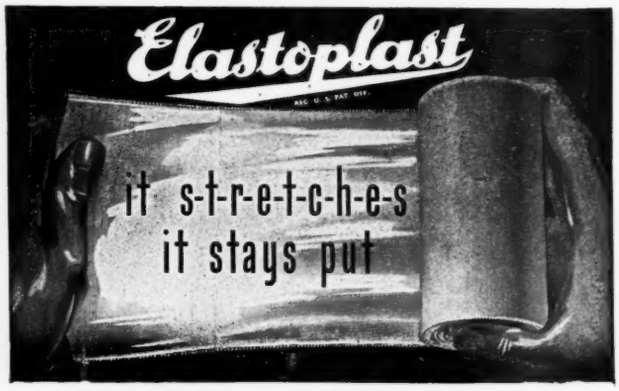

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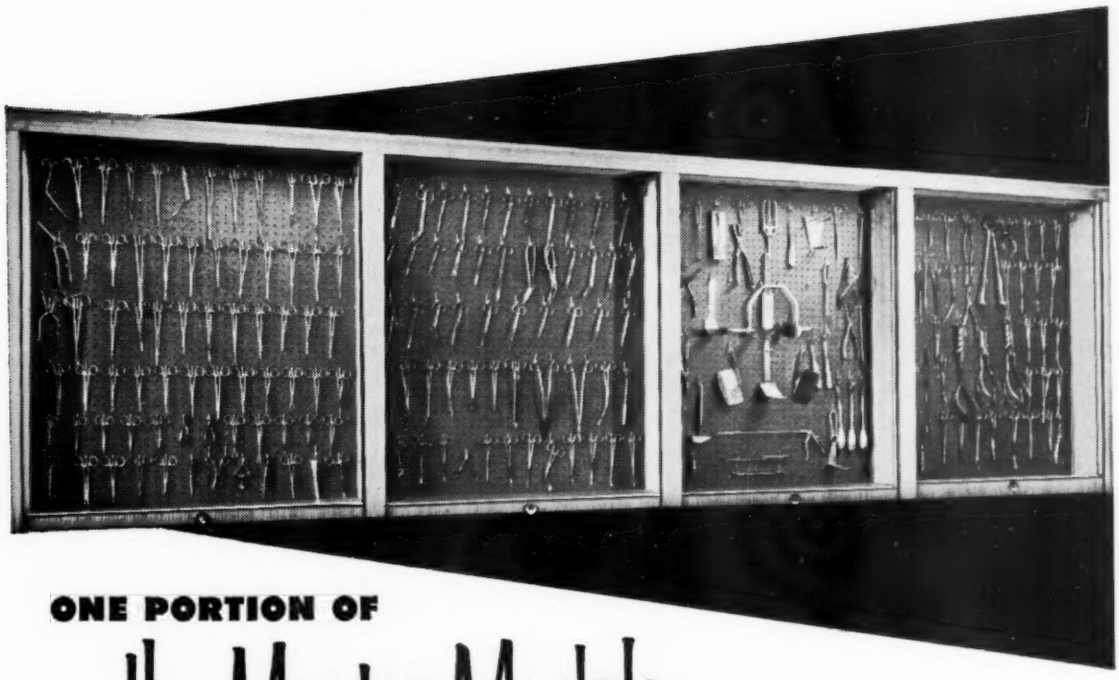

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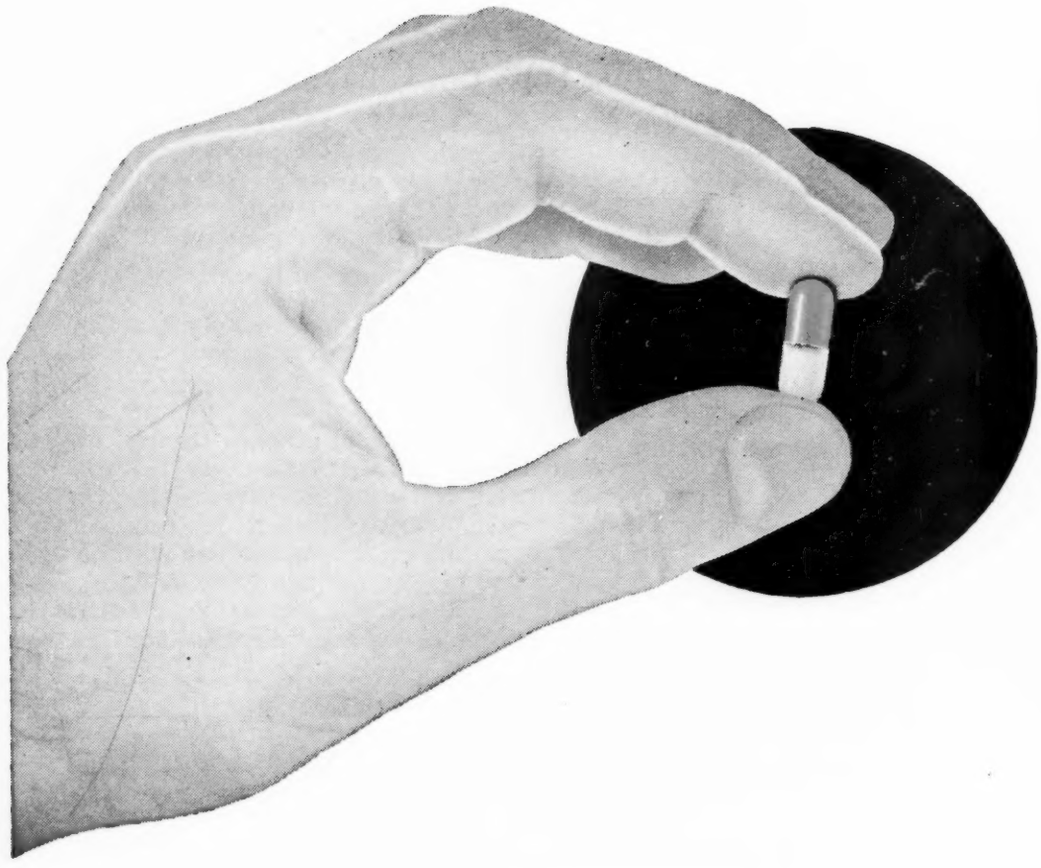

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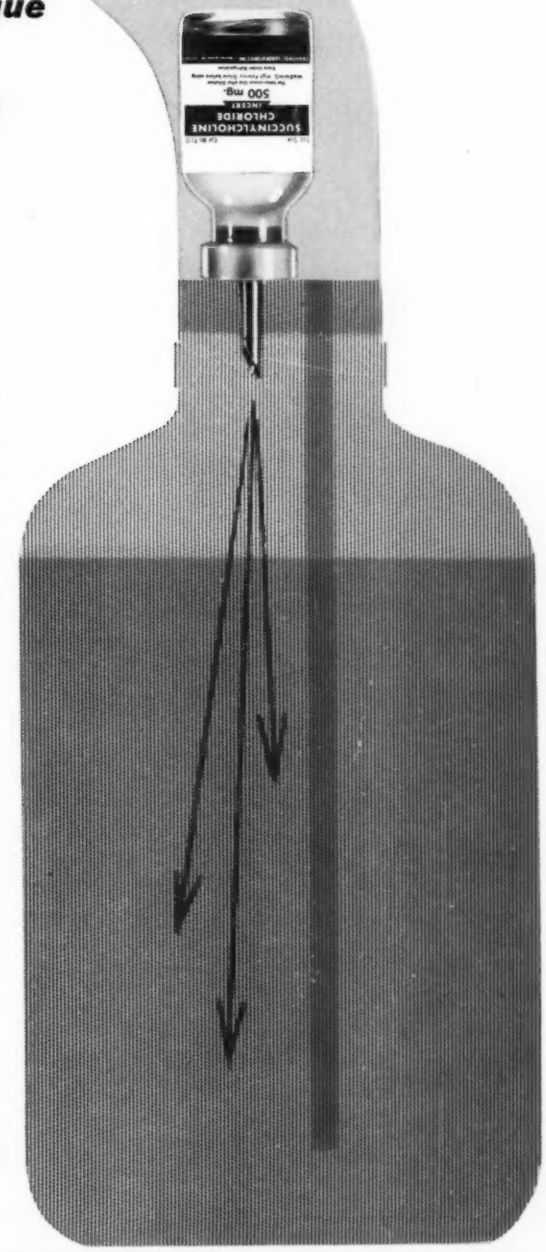

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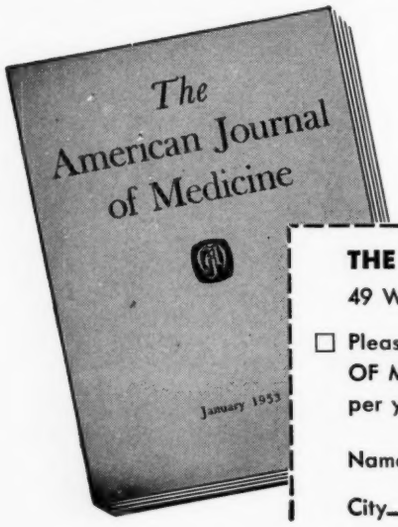

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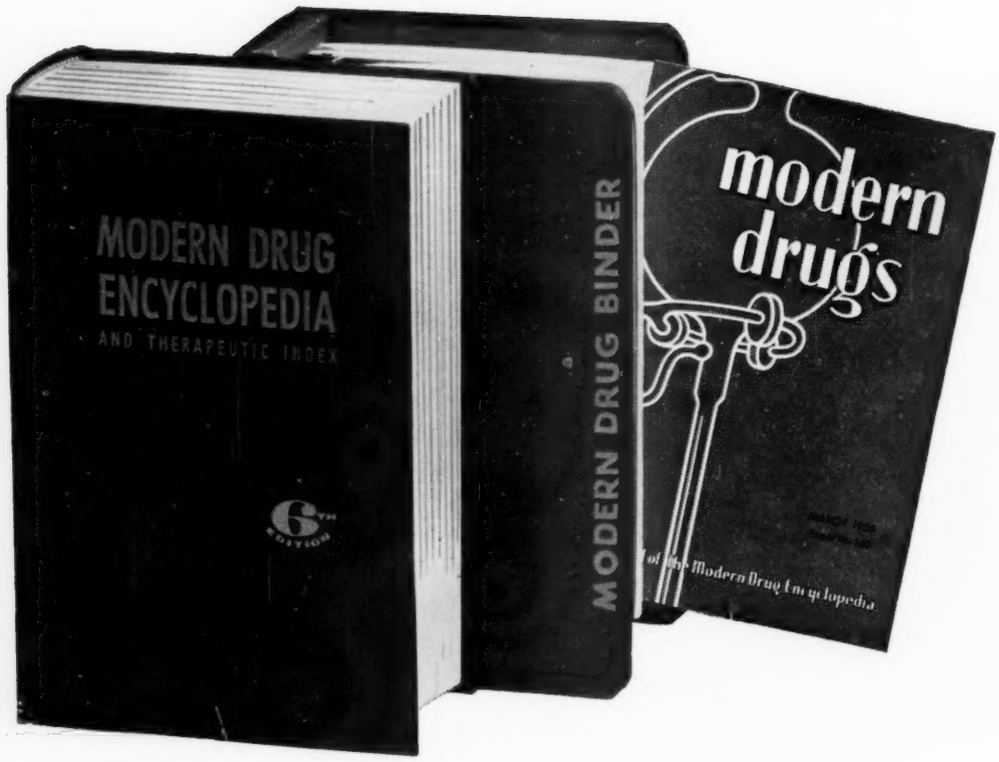

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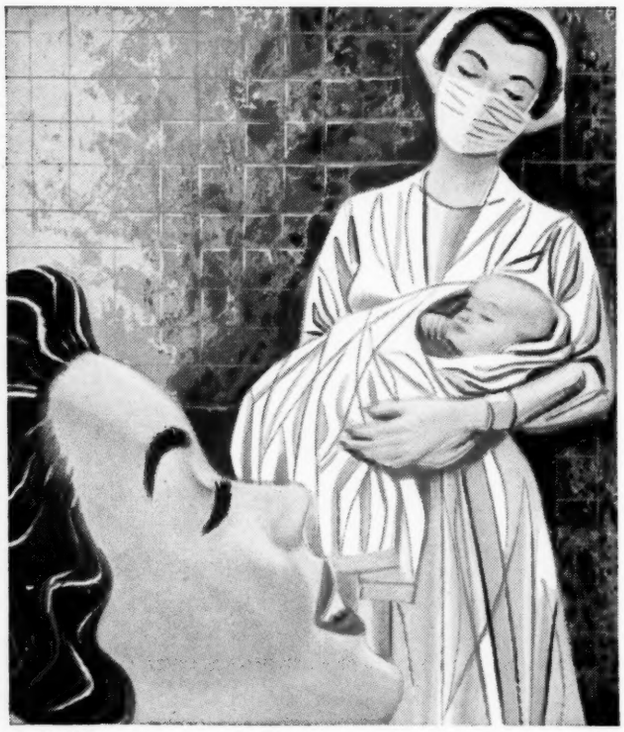

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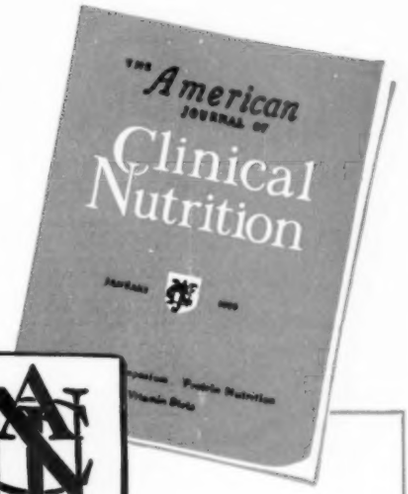

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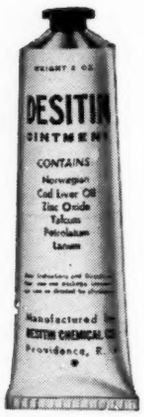

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PRESIDENTIAL ADDRESS

The Surgeon

SINCE the hour a year ago when I realized I had been made President of this surgical association until now, I have striven to understand how circumstances contrived to bestow such an honor on me. I am most grateful for that honor. I am grateful, too, to the officers and the members of the various committees who have worked so hard to make still another successful meeting. As I rise to accept the privilege, which all who have preceded me in this high office have enjoyed with such distinction, I wonder what I can say to a group of surgeons, whose interests and experience and training diverge so widely, that will be worth the saying. I have done no research. I am baffled by my problems and busy with my work as you are with yours. The things I wish to say have neither newness nor novelty to recommend them, and I am taunted by the feeling that I would not devote myself to the new had I something new to report.

I do not wish to trace the record from the time our primitive ancestors were struggling to survive in the hazardous environment in which they were cast, or to record the evolution of a single sound clinical concept from the time of its inception until it reached useful maturity. I do not wish to dwell on the fact that disease was a mystery and treatment mostly magic until a short time ago. We all know that Pasteur and Koch gave us our concept of microscopic animals and plants and in one decade, from 1870 to 1880, we learned more about health and disease than all of our ancestors had learned until then. I am sure you know that their contribution still stands in a world accustomed to airplanes and submarines, television and atomic energy, as the most momentous in all human progress.

There has been a swift flow of events in medicine since then. Precedent has come to play a smaller part in our work. Surgeons are rank individualists—we seek change and revel in it. We like to see old concepts scrapped and new ones take their place. We want new methods, new therapy and new technics. Our periodicals and our lecturers, our teachers and our texts flood us with the new. Change, constant change, is the tide upon which we ride. In a broad sense change is essential to progress. However, change and progress must never be considered synonymous.

There seem to be terminals in human knowledge: We think there are but seven primary colors. None of us expects to live to meet the man who will improve upon the multiplication table. We forget, however, that the normal in an anatomic and physiologic sense cannot be improved upon. We do not make bigger or better bodies by medical means. The inherent capacity of the heart is no greater today than it was in the time of Hippocrates or Galen. The bony framework of our body is potentially no stronger, no more resistant to injury, no more durable, flexible or lasting than that of the Greeks or the barbarians who conquered them. Normal eyes see no more and no better today than the normal eyes of all who have preceded us since the beginning of time. Man's hearing today is no better than that of the Indians who roamed the West Coast a thousand years ago. Modern medicine has come to have an appreciable insight into the normal processes of mind and body. It has been able to check

and prevent disease and in some measure to rehabilitate its victims; but it only approaches the normal, it never improves upon it. There are functional and structural end points in medicine as there are in mathematics.

A man in medicine cannot be content with tendencies and currents and generalities. His problems are specific and crucial and his capacity is always overtaxed. There was a time when the best in our profession could master the entire field, but that cannot be done today. Facts and fallacies become matted in such an inextricable way at times that men with great mental endowment find themselves hedged in by the mass of material and trussed up by dictums and slogans which have yet to gain solid ground. However, from the sick room, the morgue and our musty laboratories there continue to come more and more fragments of the eternal truth. Sound concepts are frequently displaced from our armamentarium because we have held them too cheaply or have not seen them in proper perspective. However, if their vitality is real they ultimately return.

Dare we admit that there are terminals in therapy? The amputation of a gangrenous leg may some day be performed with greater skill and less danger but it will probably remain the definitive treatment for that condition. This may also be true of the present treatment of acute appendicitis. These are terminals in therapy. Consider our concept of rest: Will chemotherapy or antibiotics or substitution therapy ever reduce rest to a subordinate place in the scheme of treatment? It is true that early ambulation is a definite improvement upon the practice of imposing prolonged rest upon our patients, but that change did not delete rest from the armamentarium of the doctor. It simply served to re-emphasize a principle which runs like the threads of a pattern through therapy. We must never lose sight of the fact that all good things in treatment do some harm, and the physician who fails to compute the harm which may come from his prescription and compare it with the good he thinks he can expect is likely to be the physician who will now conclude that bedrest is bad for the sick. Fortunately for our patients an immutable law of nature imposes some measure of rest on them when they are contending with an infected joint or a soiled peritoneum. Under many circumstances, rest and tissue repair go hand in hand. We are still trying to learn how to use it and not abuse it.

This requires timing, a faculty which is hard to acquire. There is a tempo in the course of most diseases which continues to deceive and baffle us. Often an optimum time for intervention exists in those conditions which yield to direct surgical attack. It seems to respect neither night nor day nor man's convenience. It also seems to change as our preliminary treatment improves and our technic grows better. After all, tireless attention to detail and to change constitute a team with which men in our profession must conjure.

Skill has always been considered the prime requisite of a surgeon. Few lay people know much about it and fewer know how unimportant it can be. Skill is acquired not by reading and thinking, but by practice. All surgeons begin with a full set of thumbs, and some continue to be all thumbs even though they perform remarkably good surgery. Others acquire dexterity; they groove their swing and by practice become more efficient and more rapid, although rapidity in itself is never an objective worthy of a real surgeon. Skill is the reward for repetition, and repetition can be dangerous. It is the monotonous repetition of procedure which lulls the surgeon into a sense of security and makes the most skilled the most vulnerable at times. Skill comes with time, and time has no mysterious alchemy by which it distills either wisdom or safety. Time is far more likely to harden arteries, soften muscles and dull perception. It is not dexterity but rather concentrated attention that counts in the operating room. When a surgeon is overworked or burdened by extraneous things, skill will not avail. I have seen golfers fail as the result of slight distraction and strangely enough have seen surgeons undertake most difficult tasks while lecturing or laughing.

Were a surgeon asked to designate the fault in mankind which thwarts him most often, he would point without hesitation to procrastination. Patients who die from intestinal obstruction or appendicitis die largely because of this procrastination. Cancer would be a less formidable adversary were it not possible for it to recruit procrastination as an ally and tempt its host and his attending physician to delay when immediate action is due. Surgeons are trained to make vital decisions; many while on their feet at surgery when a situation is desperate and evidence incomplete. Thus, they are probably more aware than most of the importance of an accurate preoperative study. They

know how restless a night can be when decisions thus made are still unproved and a life is still in the balance. They know too that an error in judgment is a cruel impeachment and that the necropsy they seek will yield at best some uncomfortable half-truths. They share for that reason in the common human feeling of procrastination, sometimes because they lack confidence in themselves, sometimes because they overestimate the competency of council and sometimes because they lack courage. Yet, whatever the mitigating circumstances, procrastination often makes surgery more difficult and cure less likely.

Release from pain and preservation are the dominant demands made of us by our patients. The emotional distress endured by patients between the time they first learn that surgery is necessary and the hour when they fully realize that they have survived is one form of pain which we have not learned to abate. Improvement is being made in this respect largely because our predecessors had real skill and qualities of mind and heart which over the years have continued to make it easier for our friends and even strangers to entrust us with their lives and health. It behooves us as teachers and as physicians to see to it that our successors become still more worthy of that high tribute. Confidence in us helps to dissipate fear for our patients and to allay the anguish of anticipated surgery even though fear of the unknown may still be with them. That confidence is never made more compelling by immodesty in word or conduct. Truth must color it, for its essence will always be honesty. That confidence is a tribute paid not to us so much, but rather through us to teachers and predecessors in this great field of surgery.

Judgment is the most occult and evasive of all sound surgical attributes. Some have it as an endowment, many gain it by supervision and constant association with good surgery; but whether it comes as a gift or as a reward for diligence, no man ever perfects it. Every surgeon finds that his judgment improves slowly with maturity and it is fortunate that this judgment abides as fingers become less nimble. This faculty is priceless for a surgeon, and one which must be cultivated, guarded and preserved. Caution and industry, modesty, and the discipline of unweary effort furnish the fiber which a determined devotion to detail fashions into sound surgical judgment. It is not lost until the mind which has directed skilled hands for years has faltered. We do not seek honor, glory or wealth, but rather perfection. How unbridgeable the gap between the selfish and the surgeon. We seek perfection and disregard the toll taken in its quest. Some achieve a larger measure of perfection than most, yet we all compute our efforts in terms of it. How thankful we should be that we do not have to designate who is to survive our most unpromising and courageous efforts. How thankful we should be that our opinions can be expressed freely and honestly. We follow our leaders in surgery, knowing that they may change their opinions or even reverse themselves if they think such a course will bring their goal closer. We know that they, like the rest of us, are dedicated to that which will prolong life and relieve suffering. What satisfaction it is to be in a profession in which superior men can grow to greater stature and men with less talent can augment their usefulness with honesty and industry.

Louis P. Gambee, M.D.,
Portland, Oregon

Management of Intraductal Papilloma

ITS RELATIONSHIP TO CANCER OF THE BREAST

MARTIN A. HOWARD, M.D. AND MILLARD S. ROSENBLATT, M.D., *Portland, Oregon*

DISCHARGE from the nipple is often significant as a warning that trouble may be near. If the warning is heeded, many lives will be saved; if it is ignored, many lives will be needlessly sacrificed.

At present there is a great deal of uncertainty about the significance of intraductal papilloma. There is still a wide diversity of opinion about the importance and clinical implications of this condition. Certain authors believe it is not a dangerous lesion. This may be due to the fact that both the benign intraductal papilloma and the rarer malignant papillary carcinoma may cause a serous or bloody discharge from the nipple.

The hazard of nipple discharge is great because it is so lightly regarded by so many doctors. Deaths from cancer, according to the Metropolitan Life Insurance study, in the last ten years have been reduced 11 per cent. This improvement has been credited to the educational program of the American Cancer Society, resulting in early diagnosis. Nevertheless, approximately 50,000 women die from cancer of the breast each year. It behooves us therefore to appraise, evaluate and interpret correctly nipple discharge in all diseases of the breast.

The Metropolitan Life Insurance Company has shown that early diagnosis has reduced the mortality rate. Greenwood[2] reported that in untreated carcinoma of the breast, life expectancy was only 3.8 years as compared to 12.9 years with the best treatment available. (Table 1.)

Day[3] believes the most frequently occurring cancer in women is cancer of the breast. If this condition is detected early and treated by radical mastectomy, three of every four women can be cured and lead normal lives. Deaths occur in women who delay visiting a doctor after they first discover a suspicious lump in the breast. These people fear the diagnosis of carcinoma. A tumor so neglected grows in time from a few millimeters to frequently 2 or 4 cm. or more. In general, the smaller the tumor the better the prognosis, and the larger the tumor the greater the chance of metastatic spread.

TABLE 1
LIFE EXPECTANCY

	Years of Life	Age at Death
Normal (no cancer)	19.87	73
Best treatment	12.9	68.7
Average treatment	5.78	60.7
Untreated cancer	3.8	58.3

HISTORY

In 1905 Warren[4] from Massachusetts General Hospital was the first to consider local excision of intraductal papilloma as a method of choice.

Greenough and Simmons[5] two years later also decided local excision was all that was required. However, they discovered that three of their patients had adenocarcinoma in the wall of the papillary tumor.

Judd[6] in 1917 found that 57 per cent of 100 patients with serous or bloody nipple discharge had carcinoma of the breast. The one helpful diagnostic sign in Judd's cases was a tumor mass, as every malignant tumor had a palpable mass. No mass was found in the intraductal papilloma group.

Geschickter[7] corroborated Judd's findings. Fifty per cent of his cases with serosanguineous drainage and a palpable mass were found to have carcinoma.

In 1930 Adair[8] stated that 47.2 per cent of cases of sanguineous nipple discharge were malignant. He concluded that a sanguineous discharge meant carcinoma in 50 per cent of cases and conversely, benign lesions in the other 50 per cent. It was his belief that a benign papillary cystadenoma eventually would become carcinomatous.

Haagensen, Stout, and Phillips[9] reviewed 353 cases in 1951. They believed that a serous or bloody nipple discharge might be caused from either a benign intraductal papilloma or a malignant papillary carcinoma. Benign intraductal papillomas were frequent in their series. It was their feeling that microscopic papilloma really caused bloody discharge and it was a part of a chronic cystic mastitis process, and not usually related to malignancy.

Saltztein and Pollock,[10] in reporting a series of patients with bleeding from the nipple without a palpable tumor, did not find this condition potentially malignant.

Gray and Wood[11] of the Mayo Clinic, presenting the results of their pathologic study, believed that discharge from the nipple was of great significance.

The same year Marshall and Marcum[12] found that carcinoma occurs in a significant 12 per cent of the intraductal papillomas. The discharge did not have to be bloody or the tumor palpable in all cases. The length of time the discharge had been present did not seem to make any particular difference. A palpable tumor was not present in every malignant case and the discharge was not necessarily sanguineous.

From 1945 to 1950 biopsy specimens of the breast were taken from 1,780 patients at the Swedish Hospital in Seattle, Washington. Of these, 422 (23 per cent) proved to be malignant. MacMahon found in this series that nipple discharge was a serious symptom. He believes that carcinoma will develop in 50 per cent of the patients with bloody discharge.

Chester and Bell[13] in 1951 thought that intraductal papilloma was essentially unilateral. Bell decided a bloody discharge from the nipple could well be a serious symptom. Of those patients who had bloody discharge, 6 per cent had intracystic carcinoma. He believed that carcinoma arising from intraductal papilloma was uncommon.

PATHOLOGY

Intraductal papillary tumors are proliferations of duct epithelium which project outward into a dilated lumen from one or more areas.

Haagensen has divided papillomas into two types; those evident on gross inspection and those found microscopically. Some patients may have a single papilloma while others have many. The papillomas which grow in a localized dilated portion of the duct can usually be seen grossly, and they have the appearance of a large dilated vein. They may attain considerable size and fill up the duct entirely. They may arise in more than one of the ducts. A serous or bloody discharge is usually the symptom which the patient or the physician first notices. The bleeding is often produced by injury to the papilloma; pieces of it break off inside the duct and the serous or bloody discharge carries it along the duct to the nipple. Many times we are unable to feel a papilloma, but occasionally a ridge-like elevation can be palpated along the duct. Papillomas are located in two different areas. Most of them are in the central location of the breast but a few may be in the peripheral part of the breast.

The exact relation between the single grossly visible intraductal papilloma which usually arises close to the nipple, and the smaller, especially the microscopic, intraductal proliferations which occur more peripherally in the breast is of great interest. The two kinds do not necessarily coexist in the same breast. The smaller papillomas occurring in the periphery of the breast are frequently multiple. How often these microscopic or smaller papillomas become carcinomatous is difficult to say. If carcinomatous change does occur in papillomas it is probably in this type. Several papillomas have been observed by others and by us to be degenerating, and it is possible that the small

multiple foci may well be the site of the origin of papillary carcinoma.

On study of the microscopic sections, fibrosis seems to be a prominent factor and the papillary processes seem to be due to a squeezing of the duct system by the existing fibrosis.

DIAGNOSIS

Differential. The differentiation between papillary carcinoma and intraductal papilloma is readily made both microscopically and macroscopically by most observers. The two main problems are: (1) Are intraductal papillomas potentially malignant? (2) When one removes one or more papillomas, are others present which may later undergo malignant change?

Since intraductal papilloma usually presents itself by nipple discharge it is well to consider the different causes of this emission. The five main causes are as follows: (1) chronic cystic mastitis, (2) papilloma, (3) fibroadenoma, (4) carcinoma and (5) Paget's disease.

Hinchey[14] found that nipple discharge occurred in chronic cystic mastitis and hormonal malfunction in thirty-six cases of his series (54 per cent). Seven cases (10.5 per cent) were due to intraductal papilloma, and twenty-four cases (36 per cent) occurred as a result of Paget's disease. (Table II.)

Donnelly[15] in his series discovered that nipple discharge was caused by chronic cystic mastitis in fifty-five cases (25 per cent), and by intraductal papilloma in sixty-six cases (30 per cent). Carcinoma was the greatest contributor to nipple discharge. It was the etiologic agent in ninety-eight cases (45 per cent).

Lewison and Chambers[16] studied a total of 114 cases. The etiologic agent producing nipple discharge in their series was chronic cystic mastitis, forty-six cases (40.3 per cent); chronic cystic mastitis with abscess and inflammation, six cases (5.3 per cent); chronic cystic mastitis with galactocele, two cases (1.7 per cent); fibroadenoma, eleven cases (9.7 per cent); and papilloma, twenty-seven cases (23.7 per cent). There were thirteen cases of carcinoma (11 per cent). Paget's disease of the nipple with underlying carcinoma was the background of nine cases (8 per cent).

In studying the material from Good Samaritan and St. Vincent's Hospitals it is interesting to note that of 159 cases, papillomas were associated with other benign pathologic conditions in 105 cases. It is also interesting to note that papillomas plus carcinoma with metastasis occurred in two cases, while papillomas plus carcinoma without metastasis occurred in sixteen cases. Single papilloma occurred in twenty-two cases and multiple papillomas occurred in the breast in four cases. Table III gives the exact summary of the foregoing statements.

TABLE II
BREAST LESIONS CAUSING NIPPLE DISCHARGE

	Hinchey		Donnelly		Lewison and Chambers	
	No. of Cases	%	No. of Cases	%	No. of Cases	%
Chronic cystic mastitis	36	54	55	25	46	40.3
Chronic cystic mastitis with abscess and inflammation	..	....	..	..	6	5.3
Chronic cystic mastitis with galactocele	..	....	..	..	2	1.7
Fibroadenoma	..	....	..	..	11	9.7
Papilloma	7	10.5	66	30	27	23.7
Carcinoma	..	....	..	..	13	11
Paget's disease	..	....	98	45	..	....
	24	36	..	..	9	8

TABLE III
PATHOLOGIC DIAGNOSIS

	Good Samaritan Hospital (No. of Cases)	St. Vincent's Hospital (No. of Cases)
Papilloma, single	8	14
Papillomas, multiple	2	2
Papilloma plus carcinoma with metastasis	1	1
Papilloma plus carcinoma without metastasis	9	7
Papilloma plus other pathologic conditions	46	59

Roentgenographic. The clinical diagnosis of tumor of the breast may at times be confusing and often the resulting indecision causes procrastination, not only by the patient but also by the doctor.

Cohen, Ingleby and Hermel[17] believe accuracy of diagnosis in breast lesions may be greatly increased by roentgenography. Their findings are summarized in Table IV.

Fibrocystic and other benign diseases are supposedly sharply defined by x-ray while

carcinoma is poorly defined. Scattered calcification along the ducts is thought to represent carcinoma.

Shipps[18] believes that with more x-ray experience, roentgenography should be definitely valuable in the diagnosis of breast lesions.

TABLE IV
CONTRAST DIAGNOSIS

	Clinical Diagnosis				X-ray Diagnosis			
	Correct		Incorrect		Correct		Incorrect	
	No. of Cases	%	No. of Cases	%	No. of Cases	%	No. of Cases	%
Cancer..	55	54	21	21	85	83	3	3
	26*	25*	....	...	14*	14*	....	...
Benign..	12	14	225	71	...	1..	287	91
	...	...	79*	25*	...	...	29*	97*

* Suspected cases.

MATERIAL

This paper is based upon 159 cases from Good Samaritan and St. Vincent's Hospitals. Seventy-six patients were operated upon at Good Samaritan Hospital from 1949 to 1954, and eighty-three patients were operated upon at St. Vincent's Hospital in a ten-year period from 1940 to 1950. The authors performed some of the operations; the remaining were performed by various staff members of both hospitals. The validity of the conclusions, therefore, is greater because a single surgeon did not operate on all patients.

During the five-year period from 1949 to 1954 at Good Samaritan Hospital 884 operations were performed on the breast; 201 of these were radical mastectomies. During the ten-year period from 1940 to 1950 at St. Vincent's Hospital 1,773 operations on the breast were carried out; 273 of these were radical mastectomies. In the Good Samaritan Hospital series one man had carcinoma of the breast.

Of the 884 breast operations at Good Samaritan Hospital, seventy-six patients had intraductal papilloma (an incidence of 8.5 per cent). Of the 1,773 breast operations at St. Vincent's Hospital, eighty-three patients had intraductal papilloma (an incidence of 4.6 per cent). (Fig. 1.)

The average age at Good Samaritan Hospital was 45.75 years, and at St. Vincent's Hospital 47.9 years. The youngest patient was thirteen, the eldest seventy-nine years of age. (Table v.) These patients were from all walks of life; a few of them were well-to-do, a few were from welfare service, but most of them were from the middle station in life.

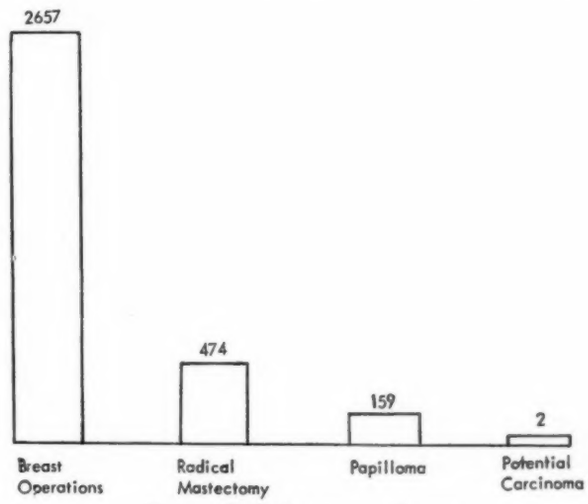

FIG. 1. Relative comparisons.

TABLE V
AGES OF PATIENTS

Ages	Good Samaritan Hospital		St. Vincent's Hospital	
	No. of Cases	%	No. of Cases	%
13 to 19	1	7	0	3.5
20 to 29	4		3	
30 to 39	18	67	16	82
40 to 49	33		30	
50 to 59	9		22	
60 to 69	7	26	7	14.5
70 to 79	4		5	

It is interesting to note that the symptoms which the patients presented in both hospital series were very similar. The symptoms could roughly be grouped in four main categories. (Table vi.) First, forty-nine patients (64.3 per cent) complained of a lump or mass in the breast in the Good Samaritan Hospital series; thirty-nine (47 per cent) had this complaint in

the St. Vincent's Hospital series. Nipple discharge accounted for forty-four cases (57.9 per cent) at Good Samaritan Hospital and forty-one cases (49.4 per cent) at St. Vincent's Hospital. Tenderness occurred in thirteen patients in both series. Deformity of the nipple was noted in only five patients at Good Samaritan Hospital and four at St. Vincent's Hospital. There were four patients with tumors discovered on examination at Good Samaritan Hospital and five in the St. Vincent's Hospital series. One papilloma was discovered during a plastic procedure on the breast.

TABLE VI
CLINICAL MANIFESTATIONS

Symptoms	Good Samaritan Hospital		St. Vincent's Hospital	
	No. of Cases	%	No. of Cases	%
Masses	49	64.3	39	49
Nipple discharge	44	57.9	41	49.4
Tenderness	13	17.1	13	15.6
Deformed nipple	5	6.4	4	4.8
No symptoms	1	1.3	..	....
Tumor discovered on examination	4	5.2	5	6

It is a well known fact that the percentage of nipple discharge and the types of discharge will vary from series to series. Nevertheless, the series from these two hospitals were fairly similar in that respect. At Good Samaritan Hospital forty-four patients (57.9 per cent) had discharge. Thirty-two patients (42.1 per cent) had no discharge. There were forty-one patients (49.4 per cent) with discharge at St. Vincent's Hospital, and forty-two (50.6 per cent) without discharge.

There are a number of different types of nipple discharge due to the variety of pathologic disturbances encountered in various series. In these two series it was found that the types of nipple discharge could be tabulated under the classifications in Table VII.

Of the seventy-six cases of nipple discharge at Good Samaritan Hospital, ten patients with intraductal papilloma also had concurrent carcinoma of the female mammary gland. Re-examination of the sections at the time this study was made failed to show any relationship between the carcinoma and the intraductal papilloma. Lehman[19] believes the carcinoma in each breast seems to start directly as carcinoma, and there was no evidence that any

TABLE VII
TYPES OF NIPPLE DISCHARGE

Types	Good Samaritan Hospital		St. Vincent's Hospital	
	No. of Cases	%	No. of Cases	%
Serosanguineous	27	37.5	26	31.5
Serous	13	17	8	9.4
Milky	..	....	4	5
Watery	4	5.4	3	3.5
No discharge	32	42.1	42	50.6

of these carcinomas had arisen in an intraductal papilloma. Radical mastectomy was performed in these ten patients.

These ten cases are in direct contrast to Marshall and Marcum's report in 1951.[12] In their series of 100 cases of intraductal papilloma, twelve cases of carcinoma occurred in the intraductal papilloma. It is our understanding that these cases were studied by Warren, and the pathologic report revealed intraductal papilloma and carcinoma simplex in four cases, and intraductal papilloma and adenocarcinoma in five cases. There were also three patients with intraductal papilloma who were diagnosed as having early carcinoma.

There were two patients in the St. Vincent's Hospital series in whom multiple small papillomas occurred in the papillary processes of the periphery of the breast. The first case was reported as a large intracystic papilloma of the breast with early malignant change *in situ*. The second patient had an intraductal papilloma with sanguineous discharge; a comment on the pathologic report follows: "While there is no penetration of the ducts, the nuclear pattern is large and shows a predisposition to malignant change."

These two cases again bring up the point that the smaller papillomas occurring in the periphery of the breast may well be more potentially malignant than the larger ones

which occur in the main ducts. In a great many of these cases we have seen a more bizarre microscopic pattern and Menne[20] believes some predisposition to malignant change is noticeable. It may be that such a common process which has been noted by Menne and others

TABLE VIII

	Five-Year Study (1949–1954) at Good Samaritan Hospital	Ten-Year Study (1940–1950) at St. Vincent's Hospital
No. of cases	76	83
Chest x-rays done	4	5
X-ray therapy	2	0
Axillary nodes palpated with carcinoma	2	2
Axillary nodes palpated without carcinoma	2	4
Recurrences	3	1

may well be a forerunner of the papillary carcinoma which is well recognized at a later time.

It can easily be seen from Table VIII that in the Good Samaritan Hospital series there were two patients in whom axillary nodes were palpated in the presence of carcinoma as well as intraductal papilloma of the breast. There were two patients in whom axillary nodes were palpated, but both of these large axillary nodes proved to be benign. In the intraductal papilloma group three patients had recurrences following surgery. In the St. Vincent's Hospital series two patients had axillary nodes which contained carcinoma and four had large axillary nodes which were palpated but were benign. One patient necessitated a second surgical procedure and another papilloma was removed.

In studying the series from the two different hospitals it is interesting to find that a different philosophy must pervade the two hospital staffs. (Table IX.) Segmental excision was carried out fifty-two times (68 per cent of cases) at the Good Samaritan Hospital, while segmental excisions were performed at St. Vincent's Hospital in only twenty-eight patients (33.7 per cent). Simple mastectomy was performed in only nine patients (12 per cent) at Good Samaritan Hospital, while St. Vincent's Hospital surgeons performed this operation thirty-eight times (45.6 per cent). It is from these two groups, when segmental excision and simple mastectomy were performed for the same lesion, that a different philosophy becomes apparent in the two hospitals. Radical mastectomy was performed in ten patients

TABLE IX
TYPES OF SURGERY

Procedures	Good Samaritan Hospital		St. Vincent's Hospital	
	No. of Cases	%	No. of Cases	%
Segmental excision	52	68	28	33.7
Bilateral excision	3	4	1	1.2
Partial mastectomy	1	1.5	10	12
Resection of nipple and areola	..	....	1	1.2
Simple mastectomy	9	12	38	45.6
Radical mastectomy	10	13	5	6.3
Plastic surgery on the breast	1	1.5	..	....

(13 per cent) in the Good Samaritan Hospital group. To repeat, the carcinoma in these ten cases was not found to be related to the intraductal papilloma. Radical mastectomy was performed five times (6.3 per cent) at St. Vincent's Hospital. Again, one case of intraductal papilloma was discovered during a plastic procedure on the patient's breast.

TREATMENT

There is a wide divergence of opinion in regard to the treatment of nipple discharge in intraductal papilloma. The subject of intraductal papilloma has been widely discussed in the literature. Lesions of intraductal papilloma, as well as nipple discharge, have been treated by many different methods. The method of choice seems to be related frequently to the custom of the consulting surgeon.

The surgical treatment varies greatly. First, there is observation, which is no treatment at all. This is especially unwise in the case of nipple discharge in which underlying carcinoma may also be present. The next form of treatment consists of a small incision with removal of a small area which contains the duct and the intraductal papilloma. The third surgical treat-

ment involves a wide wedge-shaped incision, removing the offending papilloma and several ducts. The fourth or more radical procedure, simple mastectomy, is carried out by many surgeons.

A summary of the various methods of treatment would include the following: (1) observation, no treatment; (2) semicircular or straight incision, removing duct and intraductal papilloma; (3) semicircular incision joined by straight incision; and (4) simple mastectomy, especially after the menopause.

The different surgical procedures and decisions in treatment of patients with nipple discharge and intraductal papilloma are frequently based on intangible and poorly thought-out clinical judgment. Our feelings are in accord with Campbell,[21] and Slaughter and Peterson[22] that "The diagnosis of chronic cystic mastitis, the presence of a bleeding nipple, or intraductal papilloma without cellular atypism do not indicate a prophylactic simple amputation, especially in young women."

In one patient in the St. Vincent's group, resection of the nipple and areola was performed. It is our opinion that this is rarely necessary. It is our practice to make a semicircular incision outside of the areola. The areola and nipple can then be dissected free and turned inward. The center of the curve can be joined by an incision 2 to 3 inches long extending distally from the nipple and areola. By undermining the skin, as has already been done with the areola and nipple, a segment of breast containing the intraductal papilloma can be easily removed. At times we have facilitated this procedure by introducing a probe through the duct containing the intraductal papilloma. In those patients in whom a study of the nipple and the areola is indicated, a wedge-shaped excision of the nipple and areolar tissue is usually carried out for pathologic study.

It has been our observation that the repair of the breast after the segment has been removed is not usually carefully done. If one will begin the repair of the breast tissue lying next to the pectoralis muscle and build this up using interrupted, fine catgut sutures, layer upon layer, frequently the disfigurement of the breast can be minimized if not almost prevented. It is our practice to use a subcuticular suture to close these incisions, thus avoiding the disfiguring stitch marks.

We believe that local excision is to be preferred to simple mastectomy. There is an occasional case in which simple mastectomy is properly indicated, especially after the menopause, but rarely before.

Geschickter, discussing nipple discharge as a sign of breast lesions, concludes that proper surgical investigation of the symptoms is of the utmost importance.

CONCLUSION

The problem of intraductal papilloma and nipple discharge go hand in hand. The treatment used is frequently found to be both medical and surgical, depending upon the belief and training of the individual doctor the patient contacts.

In this series of 159 cases, no actual malignancy was discovered in an intraductal papilloma. Nevertheless, one patient's condition was described as malignancy *in situ* and one other patient was noted as having abnormal intercellular change. The gravest danger is the possibility that nipple discharge may be produced by a deep-seated carcinoma of the papillary type, or that intraductal papilloma may be associated with a carcinoma.

The history and physical examination, especially the finding of a palpable mass, and perhaps x-ray diagnosis are of importance. Roentgenography of the breast previous to final consultation and advice to the patient may at times be valuable.

We believe, along with Stout, that carcinoma occurs so infrequently with intraductal papilloma that simple mastectomy is rarely indicated and radical mastectomy is never indicated unless a carcinoma is definitely diagnosed and proved by microscopic examination. Therefore, it follows that segmental resection of the involved portion of the breast with the offending duct is the procedure of choice.

SUMMARY

1. The study of 159 cases of intraductal papilloma has been made; seventy-six cases were from Good Samaritan Hospital and eighty-three cases from St. Vincent's Hospital.

2. Intraductal papilloma accompanied by nipple discharge is a confusing and frequently a poorly managed problem.

3. Carcinoma as well as benign breast disease can produce many different types of nipple discharge.

4. Only one patient's condition was diag-

nosed as carcinoma *in situ* in the intraductal papilloma.

5. One patient had atypical cellular changes predisposing toward carcinoma.

6. Segmental removal and simple mastectomy were the procedures carried out.

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DISCUSSION

H. Glenn Bell (San Francisco, Calif.): Drs. Howard and Rosenblatt have covered the subject of intraductal papilloma very well. There is very little one can disagree with, except possibly the matter of whether a wedge excision or simple mastectomy should be done.

If we are removing an intraductal papilloma because it may be precancerous, as we might remove a premalignant lesion in the bowel, then perhaps the procedure of choice would be simple mastectomy. In the series Dr. Chester and I reported before this society a few years ago, eighteen patients had simple mastectomy and of these, 40 per cent (almost half) had multiple papillomas. Eighteen other patients had simple excision; of this group, 22 per cent had multiple papillomas.

One of our patients, in whom we performed a wedge excision in May, came back the following September with more bleeding. This time she had another papilloma and infiltrating papillary carcinoma. Had this been overlooked at the first operation, or had a remaining papilloma developed into a carcinoma?

I am more inclined to perform simple mastectomy than to do a wedge excision, especially in women near or past menopause.

William H. Snyder, Jr. (Hollywood, Calif.): Drs. Howard and Rosenblatt have contributed a very worthwhile clinical study. I believe that their paper and others have established the fact that the means of diagnosis of papillary disease must rest finally on the pathologic evidence and microscopic study. Also, no clinical formula has been developed which will pick up satisfactorily all the papillomas. Probably only about 25 per cent can be diagnosed preoperatively.

I think a typical case, with discharge and with localization to an area in one of the main ducts, can be satisfactorily handled by local excision.

I think the authors have established that there is not at the present time clinical or pathologic evidence which will satisfactorily classify papilloma or papillary disease as a premalignant condition.

Strangely enough, I also studied a series of 158 cases from Good Samaritan Hospital in Los Angeles. In this series the cases were found from a study of pathologic material over a thirty-year period at that hospital, and my conclusions were quite similar. The only additional information that this series produced (and I am sorry that Drs. Howard and Rosenblatt did not have this additional material too, for it would be helpful in comparing) was that I found I could follow 79 per cent of patients for an average of a ten-year period after surgery and also find no developing carcinoma in this group.

Perhaps all this evidence then, as the years go by, will add to establishing the conclusions that Drs. Howard and Rosenblatt have made.

Alson R. Kilgore (San Francisco, Calif.): I would like to make three comments on this fascinating subject:

First, in the presence of nipple bleeding the chance of cancer being present without palpable mass is about 5 per cent. For this reason alone search for and identification of the source of bleeding is demanded.

Second, Drs. Howard and Rosenblatt report having seen only intraductal carcinoma. We have seen several instances of ordinary invasive cancer associated with benign papillary disease. In one instance a scirrhous carcinoma was found growing out from the base of an otherwise benign pedunculated intraductal papilloma.

Third, no one likes to advise a woman in her younger middle life that she has to lose a breast. However, convinced as we are that the breast which has produced papillary disease is more likely to produce cancer than the average breast, we think simple mastectomy should be considered for the woman who has been proved to have multiple papillomas, especially if in multiple ducts, and the woman who returns with bleeding after local removal of one papillary lesion.

MILLARD S. ROSENBLATT (closing): Dr. Howard and I believe that this is a controversial subject and brought it up for this reason. We are surprised we got off so lightly in the discussion because there are a great many different opinions about this subject, as judged from the philosophy of our two hospital series.

Dr. Kilgore's remarks are very much in order and we believe that we would follow the plan that he described. We are interested in a corollary of this study, namely, that in some of the cases in which simple mastectomy was performed and in some in which large wedge-shaped resections were carried out, very interesting peripheral papillomatosis was found. Dr. Menne believes that these are caused by a scirrhous or scarring-like reaction in an aging breast which causes the pinching off of parts of the ducts of the system.

I think it is possible this could be studied further, and there might be some relation to cancer of the breast from these peripheral, smaller papillary lesions just as is the case in polyposis of the colon. I think this would be an interesting subject for further discussion.

Internal Mammary Node Investigation in Carcinoma of the Breast

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THE accurate observation of the success of a method or methods of treatment for carcinoma of the breast is of paramount importance to the surgeon. The surgeon's treatment of many other neoplasms is based and evaluated on the accomplishments of therapy for the breast. The evaluation of any method of treatment for carcinoma of the breast is confused by innumerable variable factors.

The case material for this study is from our private practice in a section of the country where economic and educational standards are well above average. This immediately makes this series, as is true of most series, a selected group. It would appear that the evaluation, individual appraisal, surgery and follow-up care of each patient by one surgeon in such a series of cases of carcinoma should have great merit. The vast majority of the lesions in this series were under 2.5 cm. in diameter when the patients presented themselves for treatment. The cases reported herein will be a consecutive group, with the exception that the generally accepted criteria for operability of carcinoma of the breast were used, thus eliminating the inoperable cases. Obviously in this material there must be some rapidly growing tumors and some slowly growing ones. In some patients tumors will be lethal, while other patients will survive a normal span of years with or without treatment. We hope the types of lesions are balanced off, for if they are not our results will be misleading. The pathologic material has been examined by the Department of Pathology at the Swedish Hospital. Their decisions and interpretations of borderline lesions will affect our results. There were very few such instances, but it should be remembered that this is a small series. The gross pathologic specimens have been subjected to close scrutiny and as many as seventy-five lymph nodes have been reported and sectioned in a single specimen. The Department of Pathology has not used the method of Culbertson and Gatch,[1] which may have led to the detection of even more lymph nodes in the surgical specimen. Increased thoroughness in examination will obviously produce a greater proportion of positive nodes. The ultimate cure rate in institutions where such care is used will be higher when the regional nodes are reported as negative. Even with such thoroughness of examination many nodes which have been sectioned will fail to show evidence of metastatic disease. The work of Saphir and Amromin[2] calls our attention to the necessity of careful serial sectioning of all lymph nodes if a true picture of the metastatic status is to be obtained. This is usually not possible in a general hospital. In addition, it must be remembered that the fatty tissue, blood, and lymphatic vessels about the lymph nodes alsc may contain tumor. These sites of metastatic spread can be missed in a routine examination.

We know that the several modes of tumor spread are often overlooked because of an overemphasis on lymphatic spread. We often forget that the blood and lymphatic systems at the point of tissue-fluid movements are closely related. No doubt the explanation lies herein of the all too frequent case with a small so-called early lesion, negative lymph nodes and widespread blood-borne metastasis.

The performance of simple and radical mastectomy varies widely. Simple mastectomy involves the complete local removal of all the breast from the pectoralis major muscle including the axillary tongue of tissue. The radical breast procedure as outlined by Halstead has been used routinely in this series. This allowed an *en bloc* dissection of the axilla with little trauma and without cutting into tumor;

this would not be possible if the axilla were fixed with metastatic disease.

The primary procedure of surgery through 1951 was followed by radiation directed at the sites of local recurrence as they appeared. Prophylactic postoperative radiation therapy was not given.

This study will consider two groups of patients. One hundred consecutive cases of carcinoma of the breast seen immediately prior to 1949 were reviewed. Twelve patients who underwent simple mastectomy for medical reasons were not included in this study. The first group consists of the eighty-eight radical mastectomies for carcinoma of the breast performed immediately prior to 1949. This group has been reviewed and will serve as a baseline for conclusions to be drawn from the second group in which the identical basic factors were present such as the same type of patient with an over-all disease of approximately similar degree of spread when first seen.

The second group consisted of 141 patients in whom internal mammary node dissection was performed. The first portion of this group consisted of seventy-one mastectomies for carcinoma of the breast done in 1949, 1950 and 1951. Sixty-nine patients had radical mastectomies and two had simple mastectomies. These simple mastectomies were included because in each case the mastectomy was accompanied by an investigation and removal of lymph nodes along the internal mammary chain of the first, second and third interspaces on the operated side. It is to be emphasized that no therapeutic attempt was made when the nodes were removed. At the time this work was undertaken nothing was known about internal mammary node spread except that it occurred. The findings were reported in a previous publication.[3]

The second portion of this group consisted of seventy patients with carcinoma of the breast operated upon in 1952, 1953 and 1954. Fifty-six radical mastectomies and fourteen simple mastectomies were performed, the latter being included for the reasons stated previously. In these patients intercostal dissection with removal of lymph nodes was used as a guide for the type of operation to be performed. This procedure was considered reasonable in view of our findings upon exploring the internal mammary nodes the previous three years. The first step was taking a biopsy specimen of the questionable mass in the breast. If the biopsy revealed carcinoma, the first three intercostal spaces were explored and the lymph nodes removed along the internal mammary vessels. In many patients who have positive intercostal nodes along the internal mammary vessels, it is quite obvious grossly. In those that are questionable a frozen section of one or more nodes was taken. Patients having spread of carcinoma to these internal mammary nodes were considered unsuitable for radical mastectomy and simple mastectomy was done. This procedure was routinely followed by radiation to a bilateral sternal field and the supraclavicular and axillary field on the same side as the carcinoma. Patients having negative internal mammary lymph nodes underwent routine radical mastectomy after the method of Halstead.[4]

It is obvious that this work is too recent to draw any profound conclusions. However, questions can be asked and perhaps the trends observed will be of significance. First, is the incidence of local recurrences greater after exploration and removal of the internal mammary lymph nodes as compared with a group in which no exploration of the internal mammary chain was done? Second, did patients in the group that had intercostal lymph node removal die earlier from their carcinoma than would ordinarily be expected from a group that did not have intercostal exploration? Third, is there anything useful about intercostal lymph node investigation as a guide to the performance of simple or radical mastectomy?

By local recurrence we mean any nodule on the chest wall or skin on the operated side, excluding the supraclavicular area. This must include the skin over the sternum and in juxtaposition to the sternum. The incidence of local recurrences in patients who died or are dying from carcinoma in the eighty-eight cases having radical mastectomy without internal mammary dissection prior to 1949 was 16 per cent. The over-all metastatic disease occurring in the same period was 35 per cent. (Table I.)

In the period from 1949 through 1954 there were 141 cases in which the internal mammary nodes were explored. Positive internal mammary nodes were found in thirty-three patients (23 per cent). Negative nodes were found in 108 patients. (Table II.) Of the patients with positive intercostal nodes, only six are alive without evidence of recurrent disease. Four of

the six have been followed up only one year. One patient has survived five years and the other three years without evidence of recurrent carcinoma. (Table III.) Of those patients who died or are dying, nine have general metastasis and eighteen have local recurrence and general carcinoma. Thirty-two patients (23 per cent) had local and general disease, while twenty-three (16 per cent) had general metastasis with no local recurrence.

Thus, on comparing the two large groups (that is, the cases done before 1949 with no internal mammary node dissection, and the cases done after 1949 with internal mammary node dissection), we find that with follow-up 35 per cent of group I and 39 per cent of group II have residual disease. The increase is most marked in the number of cases having local recurrence. When one considers that 16 per cent of the earlier group have local recurrence in addition to the general disease, and that 23 per cent of the later group falls into the same category, it is noted that this is an increase of about one-third in the number of cases with local recurrences. One expects that this differential in the number of local recurrences would be even greater if the two groups had the same length of follow-up time.

TABLE I
RECURRENCES

	Per cent
No Intercostal Node Dissection (Eighty-eight Cases Prior to 1949)	
Local recurrence and general spread	1
General spread only	19
Total residual disease	35
Intercostal Node Dissection (141 Cases—1949 to 1954)	
Local recurrence and general spread	23
General spread only	16
Total residual disease	39

TABLE II
RESULTS OF INTERCOSTAL NODE DISSECTION (141 CASES—1949 TO 1954)

	Positive Nodes (33 Cases) (%)	Negative Nodes (108 Cases) (%)
Local recurrence and general spread	55	13
General spread only	27	13
Total residual disease	82	26

metastasis. It seems reasonable to believe that the four patients with positive internal mammary nodes who were followed up only one year will most likely meet the same fate as the others in the very near future. This would raise the recurrent disease and death rate even further.

Of the 108 patients with negative internal mammary lymph nodes, twenty-eight (26 per cent) died or are dying from carcinoma. Fourteen (13 per cent) had general metastasis and fourteen (13 per cent) had local recurrence and general metastasis.

For purposes of comparison, operated patients from 1949 through 1954 will be considered as a group since all had internal mammary node exploration. Of the 141 cases, fifty-five (39 per cent) are victims of residual

TABLE III
RESULTS OF THIRTY-THREE INTERCOSTAL EXPLORATIONS*

	1 yr.	2 yr.	3 yr.	4 yr.	5 yr.
Dead	8	5	6	1	..
Alive and well	4	..	1	..	1
Alive with disease	2	1	1	2	1

* Nine patients had general metastasis; eighteen had local recurrence and general metastasis.

The answer to the first question would therefore appear to be that the incidence of local recurrences was greater after exploration and removal of the internal mammary lymph nodes as compared with a group in which no exploration of the internal mammary chain was done.

The second question is concerned with the relationship of the time of death in the group that had intercostal exploration and the group that did not. It is with considerable hesitation and reluctance that we attempt to answer this question. There are so many variable factors in this small series that our deductions can certainly be wrong. We would like to compare our figures with those of another series, but the factors of variability would be even greater and perhaps of less value. Of the 141 patients repre-

sented since 1949, fifty-five are dead or are dying from carcinoma (39 per cent). This is in contrast to thirty-one patients (35 per cent) from the group prior to 1939 who died or are dying from carcinoma. From our statistical data it would appear that the group of patients since 1949 who had intercostal explorations died earlier and in a relatively larger number than those prior to 1949.

The third question concerns the usefulness of internal mammary node investigation as a guide to determine whether radical or simple mastectomy should be done in any given case of carcinoma of the breast. It is obvious that if the carcinoma has spread to the internal mammary nodes, radical mastectomy will not cure it. It is likewise obvious that the axillary spread is not altered by simple mastectomy. If carcinoma has spread to the internal mammary nodes, about 95 per cent or more of those patients will have axillary metastasis regardless of in what quadrant of the breast the primary lesion is situated. We are then confronted with carcinoma in the axilla and in the internal mammary chain, as regards the lymphatic system. The poor results obtained in radical mastectomies, when the nodes were involved with carcinoma and were matted and fixed, led Haagensen[5] and others to set up reasonable criteria of operability. Those individuals may do much better with no surgery from the standpoint of morbidity and perhaps longevity. This may also be true of x-ray therapy. With our present inadequate tools of treatment for carcinoma of the breast it seems necessary to accept radical mastectomy as the most reasonable form of surgery. From our previous study and observations and our present one we know that about half of our patients have metastatic disease at the time of surgery in the regional lymphatics. Roughly one-half of those with demonstrable metastatic disease at operation will have positive internal mammary nodes. With routine radical mastectomy we may perhaps be submitting slightly over one-half of our patients with metastatic carcinoma in the axilla to unnecessary radical surgery. The answer to our third question, based solely on our own data, would appear to be that internal mammary node investigation is interesting and an excellent prognostic guide, but should not be used as a criteria for performing or not performing radical mastectomy. For this reason, if our data are correct, the increased incidence of local recurrence cannot be justified by any apparent benefit which a patient may receive from the information obtained by doing an internal mammary node dissection.

How important a prognostic guide internal mammary node investigation is can be understood by observing that only one patient with positive nodes in this area has survived five years without evidence of demonstrable recurrent carcinoma. One patient has survived three years without evidence of recurrence while four survivors are in their first year without recurrence. The rest have died or are dying from recurrent carcinoma. If our answers to the first and second questions are correct, it would help explain this observation.

Our earlier belief that internal mammary node investigation had great merit in determining which type of operation should be carried out was apparently wrong. No surgical procedure can be justified over another if it increases the probability of failure. The dissection of the internal mammary nodes seems to have stimulated the activity of the carcinoma. It must be pointed out that doing the dissection necessitates working in carcinomatous lymphatics and the end results of increased local recurrence should have been anticipated. This, as has been previously mentioned, was found to be true in the axilla. We believe that in a great many instances cancer in the internal mammary nodes probably lies dormant unless disturbed. If it were not so, it would seem that in a greater percentage of patients with positive nodes sizable mediastinal and parasternal masses would develop. We have some autopsy evidence to bear out the observation that this does not often occur in spite of both diffuse general and local spread after operative manipulation or removal of these nodes.

Because of the apparent results of this study, future patients will not be submitted to intercostal investigation. We know now that we can expect lymphatic spread along the internal mammary chain in approximately one-fourth of our patients with carcinoma of the breast. Less than 3 per cent of the internal mammary nodes will be positive unless the axilla reveals positive nodes. Our present plan of management is to submit those patients to radical mastectomy who have a positive biopsy and who fit the accepted criteria of operability. Those patients with positive axillary nodes will be given x-ray therapy to a bilateral sternal

field and a supraclavicular and axillary field on the operated side.

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DISCUSSION

Alson R. Kilgore (San Francisco, Calif.): Most of us, I am sure, are convinced that the number of patients with cancer of the breast for whom we can accomplish complete and permanent cure is pitifully small. We are equally convinced that radical mastectomy should not be abandoned for the sake of those few who can actually be cured. The nearer we can come to selecting these curable patients for operation, the better for all and, of course, the more clearly will the effectiveness of radical mastectomy for them be apparent.

If half of all patients with axillary metastasis also have cancer in the mediastinum and if taking a biopsy of the node could exclude this group for us, we could avoid a lot of useless surgery.

However, Dr. Hutchinson, who has been working on the problem of internal mammary metastasis since the beginning of the recent wide interest in it, has become convinced that the ill effects of internal mammary biopsy outweigh its advantages. This is important information and we are indebted to him for bringing it to us.

It is to be noted with approval, I think, that he and Dr. Kiriluk have not attempted removal of the internal mammary nodes as part of a procedure intended to cure cancer of the breast. I simply do not believe that any surgical operation can eradicate all cancer from a patient when the disease has reached the mediastinum. It is perhaps sobering to reflect that surgical attack on the mediastinum was not invented by its modern proponents. If you read Dr. Emile Holman's delightful collection of excerpts from the writings of Dr. Halsted (in the September, 1955, issue of *Surgery, Gynecology & Obstetrics*) you will remember that mediastinal dissection was tried in Baltimore fifty years ago.

William B. Hutchinson (closing): I would like to thank Dr. Kilgore for his discussion.

One of the reasons we presented these data at this early time was to give the information we thought important. This may prevent others from having the same experience and making the same mistakes that we think we have made.

Cancer in the Second Breast

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IF individuals differ in their susceptibility to cancer of a particular tissue, the woman whose breast tissue has proved susceptible should have more than an average likelihood of a new cancer developing in the other breast.

Cancer in the second breast is reported to occur in from 1.5 to 9 per cent of women who have had one breast removed for cancer. This surprising variation doubtless arises in large part at least from uncertainty in determining which cancers in the second breast are independent primary growths and which are metastases from the first breast. If the two are of distinct histologic types, the problem is simple; but this is uncommon. Frequently cancer in one patient is indistinguishable from that in another. On the other hand, metastases may vary in microscopic appearance from their own primary lesions.

In many cases it is probably impossible to be categorically sure that cancer in the second breast is independent; but when its clinical course is that of a new primary lesion, it may reasonably be so regarded for practical purposes. In general we agree with the criteria proposed by Guiss[1] in a paper recently presented before this Association: (1) definite evidence that the first radical mastectomy was performed for carcinoma; (2) lapse of a period of time, preferably over two years, during which there is no sign of recurrent or metastatic disease; (3) development of a clinically independent second primary cancer in the opposite breast without any evidence of metastatic involvement elsewhere; (4) the clinical course of the patient after the second radical mastectomy must be compatible with that of a primary lesion.

We cannot quite accept the requirement that the second cancer arise two years or more after the first. For example, one of our patients underwent a second radical operation fourteen months after the first. (Both lesions were in pathologic stage I.) The woman is well thirteen years after the second operation. It is conceivable but unlikely that the second breast contained the sole metastasis from the first.

With regard to the fourth criterion, it should be recognized that early recurrence or metastasis is not necessarily inconsistent with a new primary lesion. In our total series (of unilateral carcinoma) thirteen stage I patients not only had metastases but also were dead within one year, seventeen more within two years and an additional twenty-one within three years, so that of fifty-one patients whose outlook appeared favorable metastases had occurred and the patients were dead within three years.

With these reservations we have been guided by the criteria quoted and have applied them quite strictly. Of 131 non-simultaneous bilateral cancers, nearly two-thirds have been excluded as probably part of more general spread from the first breast.

INCIDENCE IN SELECTED GROUPS

The thought has occurred to more than one that it might be possible to select from the total number of patients operated upon for cancer of the breast a much smaller group or groups in which most of the new growths in the second breast might be expected to arise. Hubbard,[2] for example, found that of twenty-four patients with non-simultaneous cancer in the second breast eleven had either a mother or sister with a history of cancer of the breast. The author suggested prophylactic mastectomy on the basis of such a family experience. Of our thirty-one patients with cancer in the second

breast, five presented such a history (including one, however, in whose mother a senile scirrhous lesion developed several years after the daughter underwent her second radical mastectomy). If Hubbard's group and ours are combined, sixteen of fifty-five (over one-fourth) had a close family history which is certainly well above the ratio for cancer of the breast generally.

Another group selection has been suggested by several, including one of the present authors[3] (A. R. K.) many years ago. Stage I patients may well have a higher incidence of cancer in the second breast simply because more of them live long enough for the new disease to arise. This thought has been pursued in the present study.

TABLE I
INCIDENCE OF CANCER IN THE SECOND BREAST (NON-SIMULTANEOUS)*

	No. of Radical Operations	Cancer in the Second Breast	Per cent
Stage I (at first operation)...	516	21	4.0
Stage II (at first operation)..	683	10	1.5
Total.....	1,199	31	2.6

* Patients whose second radical operations were performed elsewhere have been included if we could be sure that the new tumor was actually cancerous. On the other hand, 16 patients have been seen with cancer in the second breast whose first breast had been removed elsewhere. These have not been included because, of course, the total number of patients from whom they derive is not known.

MATERIAL

Our material consists of 1,850 patients with cancer of the breast seen from 1918 to December, 1949. Of these, 1,175 were seen at the University of California Hospital and Clinic, and 675 were private patients of one of the authors and his associates. Patients seen only on a "once come and go" basis with insufficient records to be significant have not been included.

From these 1,850 patients have been excluded males, inoperable cases, patients who refused operation, those first seen with recurrence, those going elsewhere for treatment, patients with simultaneous bilateral disease, those who died in the immediate postoperative period, those who for one reason or another underwent only simple mastectomy, and finally those whose opposite breasts were removed (for reasons other than cancer) either before or within a relatively short time after radical operation. Eight hundred twenty-four patients remained in the University series and 375 in the private series, a total of 1,199 patients who underwent radical operations and were exposed to development of new cancer in the remaining breast. Experience with these is summarized in Table I.

TABLE II
INCIDENCE OF CANCER IN THE SECOND BREAST AMONG PATIENTS IN STAGE I AT FIRST OPERATION

	No.	Cancer in the Second Breast	Per cent
All stage I patients.....	516	21	4.0
Stage I, living and well 3 yr. after first operation.....	390	16	4.1
Stage I, operated upon before 1940 (15 yr. or more follow-up)	162	11	6.8

Of the total of approximately 1,200, thirty-one or 2.6 per cent have developed independent cancer in the second breast according to the criteria discussed heretofore. This is probably a little more than the incidence of unilateral cancer in the general population of similar age groups. Expectancy of 1.5 to 2 per cent for women over thirty-five is approximately the generally accepted figure.*

If stage I and stage II† groups are considered separately, cancer developed in the second breast in twenty-one of 516 stage I patients (4 per cent) as compared with only ten of 683 Stage II cases (1.5 per cent).

A disappointing number of stage I patients had recurrence or died within three years. It seemed possible that a group of stage I patients

* It is impossible to determine with accuracy the incidence of cancer of the breast. It is not a reportable disease, and estimates of incidence are based on mortality statistics. However, the woman who is operated upon for cancer of the breast and dies later of a stroke or an accident is not recorded as having died from cancer of the breast.

† Stage II in this article includes all patients with pathologically demonstrated axillary metastasis.

found to be free of recurrence three years after operation might have a better outlook for long life and so present a higher proportionate incidence of cancer in the second breast than all stage I patients immediately after the first operation. The percentage remains approximately the same, however, just over 4 per cent. (Table II.)

TABLE III
INCIDENCE OF CANCER IN THE SECOND BREAST AMONG PATIENTS IN STAGE II AT FIRST OPERATION

	No.	Cancer in the Second Breast	Per cent
All stage II patients	683	10	1.5
Stage II, living and well 5 yr. after first operation	183	5	2.7

It is to be remembered that many patients in the series are still living and exposed. Carcinomas in the second breast arise after intervals as long as ten, fifteen, twenty or even more years. Patients whose first breasts were removed as late as 1949 have been exposed to development of a new primary lesion for only five years; even those patients operated upon in 1944 only ten years. Of our stage I patients (who remained without recurrence three years after operation), 162 were operated upon fifteen or more years ago. Of these, cancer developed in the second breast in eleven or 6.8 per cent. (Table II.) Although the total in this group is admittedly too small for accurate statistical evaluation, nevertheless a substantial correction for future cases, probably of about this order, is indicated.

Dobson[4] has suggested that, in addition to stage I patients, those patients in stage II with no recurrence after five years be offered prophylactic mastectomy. In our experience, cancer has developed in the second breast in only 1.5 per cent of all stage II patients because, of course, so many of these patients die of their first breast disease before the second lesion has time to appear. In the much smaller number of patients who remained well five years after the first operation, the proportionate incidence of cancer in the second breast has been higher (2.7 per cent, Table III) but still not as high as among stage I patients.

SURVIVAL RATES

As Guiss has pointed out, not all patients who have cancer in the second breast die of it, so that it cannot be said that six deaths from cancer would be prevented by doing prophylactic mastectomy on 100 stage I patients. Guiss, Harrington[5] and others have reported very favorable survival rates for patients with bilateral non-simultaneous cancer, and the former has advanced the suggestion of " . . . a humoral reactivation of the body defences against cancer by the development of the secondary lesion." We find this hard to accept with its thesis, implied at least, that a second cancer may be a good thing to have. It should be noted that the substantially better survival rates for patients with bilateral non-simultaneous radi-

TABLE IV
SURVIVAL RATES FOLLOWING RADICAL MASTECTOMY (HARRINGTON[5])

Unilateral		Bilateral Non-simultaneous			
Years after Operation	Survival Rate (%)	Survival Rate after First Operation		Survival Rate after Second Operation	
		Yr.	%	Yr.	%
15	25.1	15	35.1	15	19.4
20	17.6	20	24.1	20	15.8

TABLE V
FIVE-YEAR SURVIVAL FOLLOWING SECOND RADICAL MASTECTOMY (FOLLOWED UP TO 1955)*

	Total	Living and Well 5 Years
Second breast stage I	13	8
Second breast stage II	8	3
Total	21	11

* The 31 cancers of the second breast (see Table I) are from the total group of 1,199 radical mastectomies performed before 1950. Ten of these second cancers have appeared since 1950, leaving 21 of minimum 5-year observation since second operation.

cal mastectomy are calculated from the date of the *first* operation. However, women in whom cancer develops in the second breast have already enjoyed some and often many years of survival from the first. After a new cancer has developed, it is survival from this that is of interest to the patient. We think that if survival rates are calculated from the date of the second operation, they will be found not to differ greatly from those for unilateral cancer in general. (Tables IV and V.) The fact that cancers in the second breast run courses consistent with new primary tumors is one of the very reasons for so regarding them.

Details of the thirty-one patients with cancer in the second breast are shown in Table VI.

TABLE VI
LIST OF PATIENTS WITH CANCER IN THE SECOND BREAST

Year of First Operation	Age (yr.)	Interval between First and Second Cancers (yr.)	Stage at Second Operation	History after Second Operation
Stage I at First Operation				
1919	63	9	I	D.I.D., *2 yr.
1927	48	13	I	Well, 15 yr.
1927	68	9	I	D.I.D., 9 yr.
1928	55	7	II	D.Ca.,† 2 yr.
1931	33	19	I	Well, 5 yr.
1932	46	1½	I	D.Ca., 5 yr.
1933	49	3	II	Well, 15 yr.
1935	57	2	II	Well, 18 yr.
1936	36	7	I	Well, 12 yr.
1937	48	18	II	Second operation, Dec., 1955
1938	59	6	I	D.Ca., 8 yr.
1940	55	5	II	D.Ca., 5 yr.
1941	47	1½	I	Well, 13 yr.
1942	37	6	II	D.Ca., 3 yr.
1943	75	2	I	D.Ca., 2 yr.
1944	49	10	I	Well, 2 yr.
1945	50	7	II	Well, 2 yr.
1945	50	3½	I	Well, 6 yr.
1946	48	3½	II	Well, 5 yr.
1947	43	5½	II	Well, 3 yr.
1948	64	4	I	Well, 3 yr.
Stage II at First Operation				
1929	32	6	II	D.Ca., 1 yr.
1941	52	9	I	D.Ca., 1 yr.
1942	51	3	I	Well, 9 yr.
1942	67	2	II	D.Ca., 1 yr.
1944	37	10	I	Recent case
1945	72	5	I	D.I.D., 1 yr.
1947	52	6	I	Well, 1 yr.
1948	45	6	I	Well, 2 yr.
1949	46	1½	II	Well, 4½ yr. (Dec., 1955)
1949	49	5	I	Recent case

* D.I.D. = Died of intercurrent disease.
† D.Ca. = Died of cancer.

COMMENTS

In this study emphasis has been laid on the possibility of selecting a group or groups, smaller than the total number of patients with cancer of the breast, in which the majority of cancers may be expected to arise in the second breast. The experience recorded indicates that a stage I patient has substantially greater chance (probably about three times greater) of developing independent cancer in the remaining breast than the average woman has in *either of her two breasts.*

Whether it is worth while in a selected group such as this to subject fifteen or twenty women to simple mastectomy to save one from having a new cancer and from a second radical mastectomy may be open to debate.

Women vary in attitude toward loss of a remaining breast. Some think that they would be almost de-sexed or they have great reluctance to undergo another surgical experience, even a minor one. Others think it worth while to lose the second breast for whatever additional safety this may offer and for freedom from some anxiety about the possible appearance of a new cancer. A few even welcome it for cosmetic reasons. We think an intelligent, well balanced woman is entitled to decide for herself on the basis of the most nearly accurate facts we can give her.

SUMMARY

1. After 1,200 radical mastectomies, cancers behaving like independent growths have developed in the second breast in thirty-one patients (2.6 per cent) so far. It is to be expected that additional cases will yet appear among patients in the series who are still living.

2. In a selected group (stage I), cancer has developed in the second breast in 4 per cent. Corrected for future cases among patients still living, the eventual incidence will apparently rise to about 6 per cent, roughly three times the general incidence of unilateral cancer.

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DISCUSSION

Leonard Dobson (San Francisco, Calif.): In 1921 Dr. Kilgore published a paper entitled "The Incidence of Cancer in the Second Breast" (*J. A. M. A.*, 77: 454, 1921). He had studied 1,100 cases of cancer of the breast, combining a series of cases from the Johns Hopkins and the University of California Hospitals. Now, Drs. Kilgore, Bell and Ahlquist have given us a report on the same subject based on an analysis of about the same number of cases. In spite of the conservatism brought by thirty-five years of experience the conclusions are essentially the same, namely, that in 4 to 6 per cent of patients who have had stage I carcinoma of the breast a new cancer later develops in the second breast. This is three to four times the incidence of unilateral cancer of the breast.

Whether the incidence of a new cancer arising in the second breast is 2 per cent or 9 per cent, the fact remains that there are patients who have been cured of their first cancer only to die of cancer arising in the remaining breast. During this past year I have seen three patients who come in this category. Many patients who have had cancer of one breast are not more alert to discover a tumor in the second breast, and sometimes their doctors also miss the new growth.

The statement is made that this article is a study of facts and is not a plea for prophylactic mastectomy. However, it seems to me that the facts show lives can be saved by performing a prophylactic simple mastectomy in *selected* cases. Such cases would include those patients with a strong family history of cancer of the breast and whose cancer was stage I. I would add to this group stage II patients who have gone more than five years without recurrence or metastases.

If the doctor is convinced of the value of prophylactic simple mastectomy in selected cases, he should present the facts in a cool manner and not as an enthusiastic advocate. The doctor should establish good rapport with the patient and should understand her personality and prejudices before mentioning the subject of amputation of the second breast.

I endorse the statement in this paper: "We think an intelligent, well balanced woman is entitled to decide for herself on the basis of the most nearly accurate facts we can give her."

Herbert Willy Meyer (New York, N. Y.): I think the papers by Drs. Howard and Rosenblatt, Drs. Hutchinson and Kiriluk, and Dr. Kilgore and co-workers are extremely valuable. Certainly we can easily correlate what Dr. Kilgore brought up, concerning bilateral carcinoma of the breast, with Dr. Howard's paper. If a patient has diffuse papillary disease in one breast, there is the likelihood that the disease or symptoms of it will also develop in the opposite breast. Drs. Hutchinson and Kiriluk's paper confirms my opinion that research work on ultra-radical surgery for carcinoma of the breast should go on, and it should continue in only a few clinics where all the facilities are available in order that the patients may have the very best treatment.

I think it would be most unfortunate if the average, casual general surgeon were to follow this ultra-radical surgery in institutions where if such surgery is done the mortality rate of the good radical mastectomy will be increased. It will give ammunition to the medical men and to some of the surgeons and general practitioners to follow the advice of Bruce and McWhirter of simple mastectomy as the method of choice in the treatment of carcinoma of the breast, followed by radiation.

On the one side we have the ultra-radical surgeon; on the other side we have the ultra-conservative surgeon. By and large, until we have found a better method of treatment for carcinoma than surgery, a good radical mastectomy performed with all of the principles of good cancer surgery will in the long run give the best results for suffering women and men.

Allen M. Boyden (Portland, Ore.): With reference to the paper by Dr. Kilgore and co-workers, I wish to mention one interesting case in point. A doctor upon whom I had performed radical mastectomy inquired about the advisability of simple mastectomy on the second breast. I referred her to Dr. Kilgore's previous studies in this regard. It was her decision to lose the second breast. Perhaps if more patients had a scientific background and understanding, they would choose the same.

Ralph H. Loe (Seattle, Wash.): Dr. Kilgore's paper is intriguing, but I am not quite sure that I can agree with him unless he can answer the following question:

If we are going to advocate simple mastectomy of the uninvolved breast on the basis of the incidence of subsequent cancer in that breast, we ought to know what the incidence of carcinoma is elsewhere in the body in this same group of patients. Is there a higher incidence of carcinoma of the colon, bladder and so forth in a patient who has undergone radical mastectomy? I have had several patients who have had carcinoma of other organs and also carcinoma of the breast.

LEWIS W. GUISS (Los Angeles, Calif.): Dr. Kilgore's figures on the incidence of the second carcinoma following radical mastectomy for a first in a way gratified me because they correspond so closely with the figures we have compiled in Los Angeles.

Dr. Seabrook made a study in Portland with similar results, and I have had a discussion with Dr. Danely Slaughter who reworked the material at Illinois Research. It pretty much boils down to the fact that the incidence of second mammary carcinoma is 3 per cent or less.

Dr. Kilgore and co-workers leave to the patient the decision of whether or not prophylactic simple mastectomy should be performed on the second side. I wish it were as easy as that. At least in my practice, the patient leaves the entire decision to me. I may present the facts to the patient in an impartial manner; and when we get all through with this impartial presentation, the patient says, "What shall I do about it"? Therefore I think the decision is going to have to rest in the doctor's hands and not with the patient. On the basis of what has been presented and the other figures which I have assembled, it is still difficult, if not impossible, for me to suggest the application of the prophylactic simple mastectomy on the remaining breast.

ALSON R. KILGORE (closing): In answer to Dr. Loe's question, our records show that among the 516 stage 1 patients, in twenty-one of whom cancers have developed in the second breast, two cancers of the rectum, three cancers and one "malignant polyp" of the colon, two primary bronchogenic cancers, and one each of the stomach and ovary (a total of ten in various organs aside from the breast) have appeared after intervals of one to fifteen years.

Spontaneous Regression of Malignant Tumors

REPORT OF A TWELVE-YEAR SPONTANEOUS COMPLETE REGRESSION OF AN EXTENSIVE FIBROSARCOMA, WITH SPECULATIONS ABOUT REGRESSION AND DORMANCY

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MALIGNANT tumors vary greatly in their rate of growth. Some have periods of very slow growth and then grow rapidly. Some are slow to metastasize or their metastases lie dormant for many years. Then there are some that have completely regressed although untreated.

The older literature contains many accounts of "spontaneous cures," but in most cases adequate histologic examinations are absent or the follow-up periods have been too short to carry much conviction. During the past twenty-five years, however, a considerable number of bona fide cases of spontaneous regression, partial or complete, have been reported. We wish to report the case of a thirteen year old girl who had an extensive fibrosarcoma when five months of age; she received no treatment and now is entirely well.

CASE REPORT

Patient S. V. was first seen in Stanford Hospital on May 5, 1943, at the age of five months, because of a large tumor in the left upper thigh and lower abdomen. When the baby was two months old, her mother had noticed a lump in the left inguinal fold. This mass had grown steadily, had bulged out the inguinal fold and had produced a marked swelling of the upper left thigh. She had been a feeding problem since birth, with a great deal of colic and constipation. Several days before admission she began to have frequent green, watery stools containing undigested food.

There was no fever on admission but on the fifth and sixth days her temperature rose to 38.5°C.

Examination showed a well nourished, well developed baby five months of age. The upper left thigh was about 50 per cent larger than the right, and on palpation there was a 9 by 7 cm. rather soft, deep-seated mass extending downward below the left inguinal ligament. Abdominal palpation revealed a firm, fixed mass extending upward from the left iliac fossa laterally in the flank to above the left costal margin. The mass in the thigh seemed to be an extension of the abdominal mass.

Laboratory studies included the following: *Blood counts:* May 7, 1943—erythrocytes 4,320,000, hemoglobin 14 gm. per cent, 69 per cent Sahli, leukocytes 7,400, neutrophils 41 per cent, eosinophils 2 per cent, lymphocytes 51 per cent, monocytes 6 per cent. May 11, 1943—leukocytes 11,600, neutrophils 46 per cent, eosinophils 1 per cent, lymphocytes 53 per cent. *Urinalysis:* May 7, 1943—no albumin, no sugar, no casts, rare red blood cells, 2 to 4 white blood cells per high power field. *Tuberculin test:* May 10, 1943—$\frac{1}{1000}$ OT. negative at twenty-four and forty-eight hours. *Sedimentation rate:* May 10, 1943—22 mm. in 60 minutes (Wintrobe). *Stool culture:* May 10, 1943—"No members of the typhoid, paratyphoid, or dysentery group were isolated." *X-ray examinations:* May 7, 1943—the patient's chest was clear. The soft tissue mass was noted in left upper thigh. Excretory urograms showed both kidneys were functioning well. There was a large mass filling the left flank and iliac fossa, displacing the descending colon and small bowel to the right, and pressing on the left side of the bladder. (Figs. 1A and B.) The diagnoses considered at that time were: (1) sarcoma of some type, (2) hemangioma or lymphangioma and (3) lipoma.

A few days later the inguinal mass was aspirated to rule out a psoas tuberculous abscess but no pus was found.

On May 15th the mass in the thigh was biopsied through a long incision. It was planned that if the tumor should prove to be benign, the incision

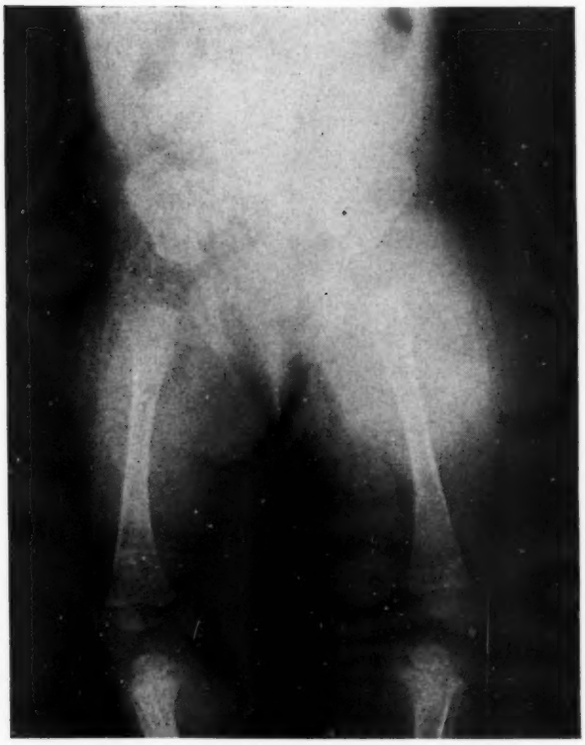

FIG. 1A. X-ray on admission (May 11, 1943) shows the large soft tissue mass in the upper left thigh and groin.

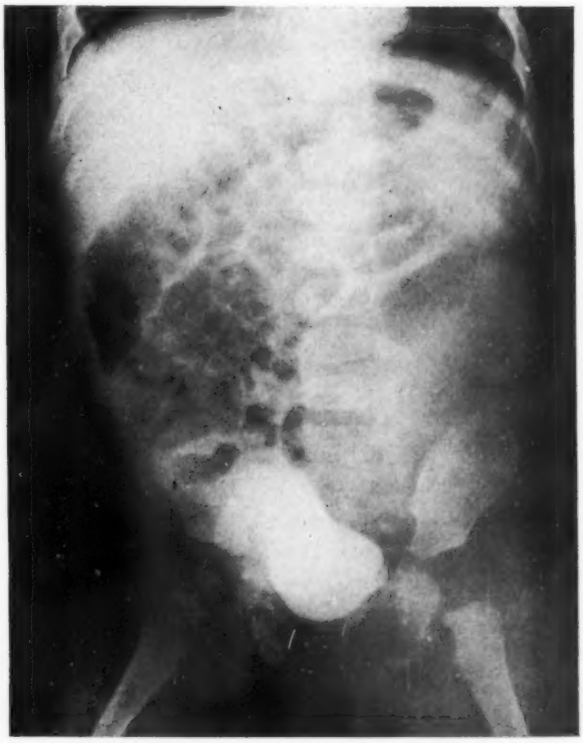

FIG. 1B. Intravenous pyelogram (May 11, 1943) shows good function of both kidneys and the large mass situated posteriorly in the lower left abdomen and left flank. The mass displaces the descending colon and small bowel to the right and presses on the left side of the bladder.

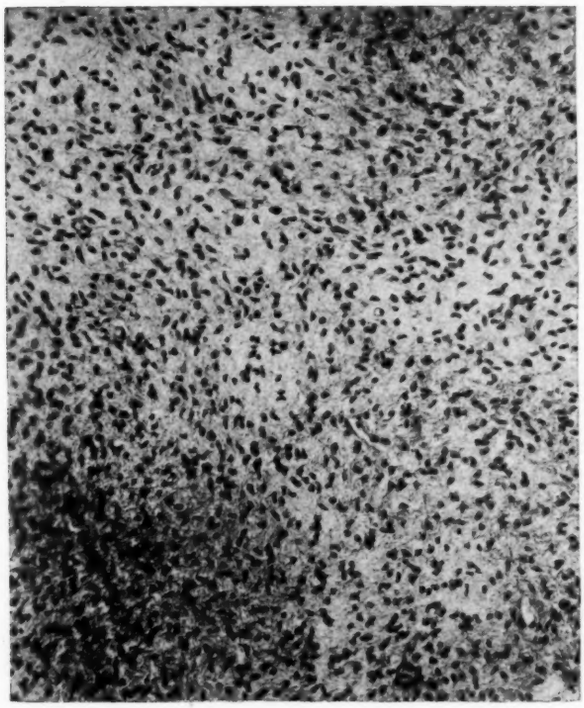

FIG. 2A. Low power view of the tumor.

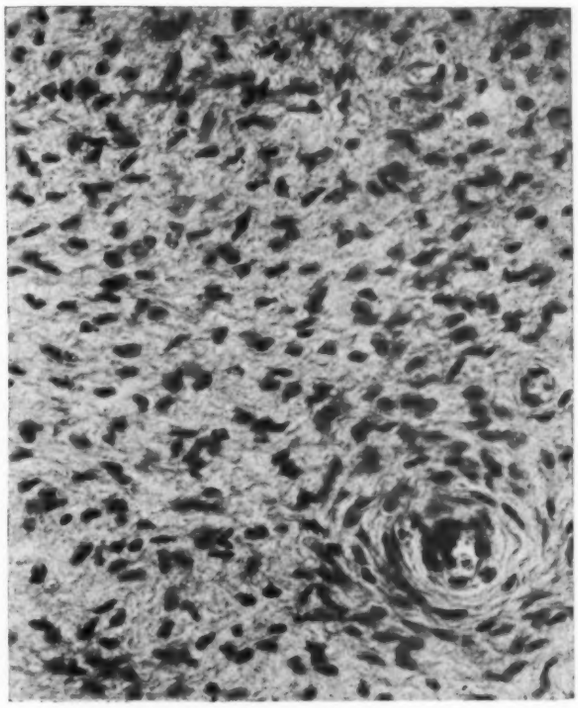

FIG. 2B. Higher power view of the tumor.

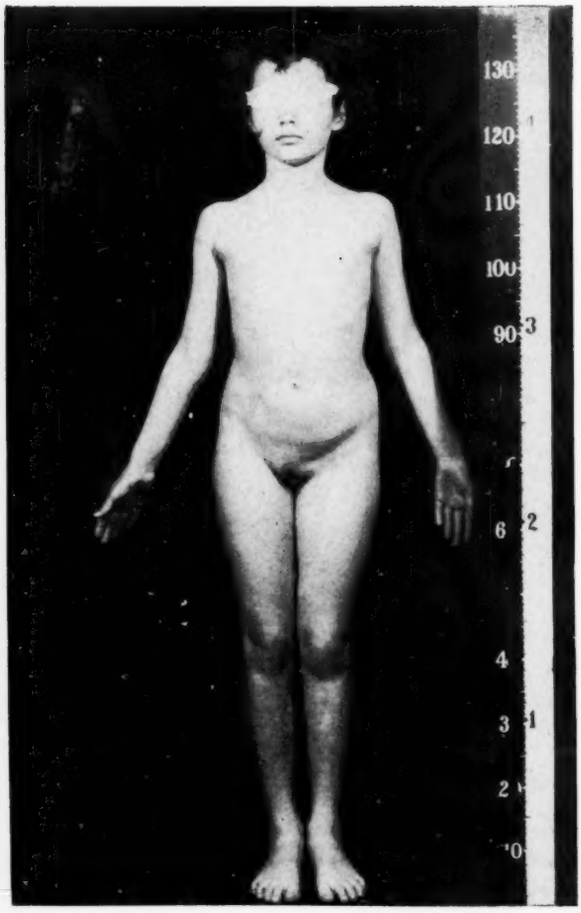

FIG. 3A. Photograph of the patient at ten years of age; biopsy scar in left upper thigh. Note patient's normal general development for that age.

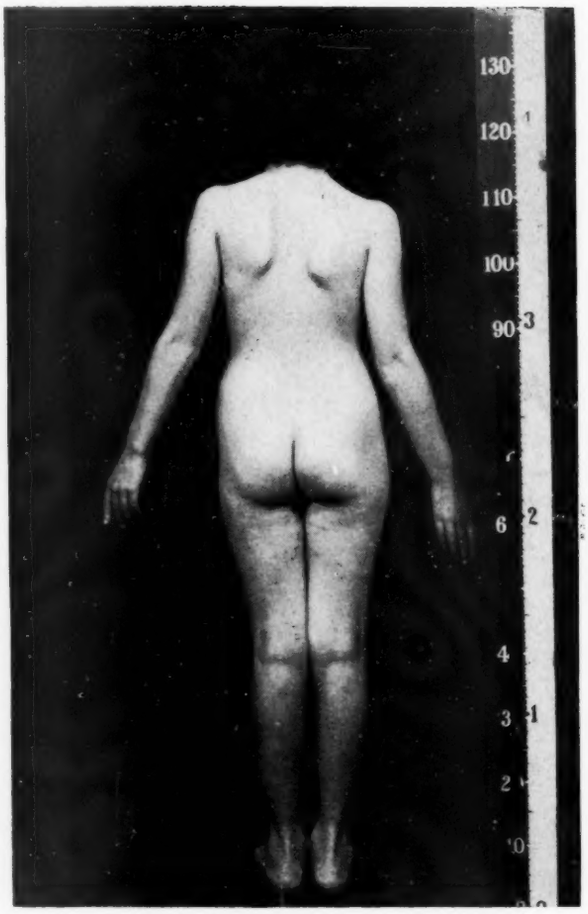

FIG. 3B. Slight scoliosis can be seen.

would be extended upward across the inguinal ligament and flank. A diffuse, pink, vascular tumor was encountered which was invading muscle and had surrounded femoral vessels and nerve. A frozen section was examined and found to be a malignant tumor, some type of a spindle-cell sarcoma. Since it was impossible to remove the tumor, the wound was closed.

The report on the permanent sections and special stains is as follows: "Gross Specimen: Consists of a small wedge-shaped piece of pale grayish-white tissue which has the appearance of 'fish flesh.' It measures $1 \times 0.8 \times 0.4$ cm, and is soft and semitranslucent.

"Histological Examination: Sections show tumor of rather uniform structure consisting of loosely grouped, small spindle-shaped tumor cells with small, oval to polygonal nuclei. There is considerable fine fibrillary material and reticulated stroma between the tumor cells. Mitotic figures are not numerous. (Fig. 2A and B.) Van Gieson's stain shows slender fibers of collagen between the tumor cells. Mucicarmine stains reveal nothing in the matrix indicative of mucin. The diagnosis is sarcoma, thigh, fascial (fibrosarcoma)."

The subsequent week the case was presented to the Stanford Tumor Board. It was decided not to use x-ray therapy because the sarcoma was well differentiated and unlikely to respond to radiation; a high dose over so large an area in the abdomen and thigh could not be borne. A safe dose would have been ineffective and would merely have made the baby very sick.

The baby's temperature rose to 38.8°C. for two days postoperatively, then dropped to normal. No treatment was given unless the operation for the biopsy under general anesthetia and several x-ray examinations can be considered forms of therapy.

The skin sutures were removed on the seventh postoperative day and the baby was sent home with the wound healing satisfactorily. Her parents were given a hopeless prognosis. We expected that within a short time the rapidly growing sarcoma would produce a fungating mass in the groin or flank.

Two months after operation, however, we found

FIG. 4A. X-ray taken at examination, July 10, 1955. Note that the asymmetry of the iliac wings has persisted since 1943. The radiolucency of the left iliac crest also persists. The pedicles on the left of L3, L4 and L5 are small and sclerotic.

FIG. 4B. Note the expansion of the spinal canal and the hollowing of the posterior surface of L3, L4 and L5.

the wound well healed and the tumor no larger. Four months postoperatively we thought the abdominal and thigh masses were both a little smaller.

The child was followed up regularly and the masses continued to recede until eighteen months after the biopsy when no masses were palpable. She had begun to walk at thirteen months of age.

We have seen her at yearly intervals. X-ray examinations have been made many times, the last being in July, 1955. On five occasions she has been presented before the Stanford Tumor Board as having a rare case of spontaneous regression of a malignant tumor.

The microscopic sections have been examined by at least fifteen pathologists in two medical schools. New sections have been cut and special stains made on several occasions. All pathologists agree on the diagnosis: malignant fibrosarcoma.

In studying the case report of Cushing and Wohlbach[2] it was noted that the biopsy specimen of the malignant paravertebral sympathicoblastoma had been diagnosed as a spindle-celled sarcoma. That child was treated with Coley's toxin. Ten years later a laminectomy was performed and the tumor proved then to be a benign ganglioneuroma.

To determine if our patient's tumor could have been similar to that described by Cushing and Wolbach,[2] more special stains have been made recently. However, these stains give no cause for disagreement with the original diagnosis of fibrosarcoma.

On the most recent examinations in July, 1955, the girl was healthy and showed the normal secondary sex characteristics of a girl nearly thirteen years of age; her menstrual periods had begun. There were no neurologic changes and no palpable masses. Her only complaint was occasional slight pain in her left hip when performing certain acrobatic dances. Figure 3A and B show the girl's appearance at the age of ten. She declined to be so photographed in July, 1955.

The x-ray examinations over the last five years are all similar except for normal bone growth. (Fig. 4A and B.) There is an asymmetry of the iliac wings, the left being somewhat displaced laterally and inferiorly; there is an irregular area of radiolucency along the left iliac crest posteriorly which has the appearance of having been caused by a soft tissue pressure erosion. A lateral view of the lumbar spine shows expansion of the spinal canal with hollowing of the posterior surface of L3, L4

and L_5 vertebral bodies. The pedicles of these vertebrae on the left are small and sclerotic.

COMMENTS

Many of the cases reported as "spontaneous regression" cannot be accepted. We believe that there should be a set of standards for the reporting of such cases. Such a set of standards for complete spontaneous regression should include the following questions:

Criteria for Spontaneous Cure

1. Was the histologic examination adequate? Several pathologists should examine the microscopic sections independently. "Metastases" should be biopsied to prove that they are indeed metastases.

2. Have the tumor and metastases disappeared completely?

3. Was any treatment given? No treatment of any kind should have been given if regression is to be called spontaneous.

4. Is the follow-up period sufficiently long for the particular tumor? One would like a follow-up period of at least ten years.

Many tumors can occasionally show very long latent periods (carcinoma of the breast and melanomas of the choroid and skin are examples). This fact must be considered before reporting a "cure." Willis[29] lists the wide range of dormancy for certain tumors as follows:

TABLE A
CLINICALLY DORMANT PERIODS

Site	Latent Period (yr.)
Breast (carcinoma)	6–20
Cutaneous and ocular melanoma	14–32
Kidney (carcinoma)	6–8
Tongue (carcinoma)	8–15
Stomach and colon (carcinoma)	5–6

Criteria for Complete Spontaneous Cure Applied to This Case

1. Was the histologic examination adequate and correct? Over the past thirteen years sections of the tumor in this case have been examined by more than fifteen pathologists, including the pathology staffs of two medical schools. The block has been recut and new sections stained on several occasions. All pathologists have agreed that this was a malignant tumor—a fibrosarcoma.

2. Has the tumor completely disappeared? During the first three years the baby was seen every three months, then every six months, and the last five years once a year. The child has had complete physical and x-ray examinations repeatedly, the most recent in July, 1955. The defects noted in the lumbar vertebrae and the deformity of the pelvis have persisted but there is no visible bone invasion. The defects are believed to be due to atrophy from pressure by the tumor. When the tumor disappeared, it left a shell of compressed bone which has not changed in twelve years.

The child has been repeatedly examined by the Stanford Tumor Board. She has no pain anywhere, no masses are palpable, there are no neurologic changes and she has developed normally, both mentally and physically, for a thirteen year old girl.

3. Was any treatment given? The tumor was obviously inoperable and no attempt was made to remove it. No x-ray or any form of therapy was given.

4. Is the period of follow-up sufficiently long? We have waited two years past the arbitrary ten-year limit. Still no recurrence has appeared.

SPONTANEOUS REGRESSION OF MALIGNANT TUMORS

The literature dealing with the great variability of the rate of growth of malignant tumors is extensive. Ewing[4] accepts a number of cases as genuine spontaneous regressions. He stated that the majority were either not well documented or had received some form of treatment. Willis[28,29] also accepted it as a fact that the retrogression of malignant tumors rarely occurs. Shimkin[22] states: "Even complete regressions of fully developed cancer, without recurrence and without therapy have been recorded, although acceptable cases of this type are medical curiosities."

In 1918 Rohdenburg[21] collected 302 cases of temporary or permanent recession of malignant growths. His is probably the most exhaustive study that has been made of the fluctuation of growth energy of malignant tumors. Rohdenburg attempted to segregate cases of complete recession from partial recession, and those proved histologically from those open to question. He lists forty-two cases of "complete recession of malignant tumors, carefully con-

trolled." A study of these cases, however, reveals that there are only a few in which microscopic appearance of malignancy was well attested, no treatment of any kind was given, and in which a careful follow-up over several years showed no local recurrence or metastases. Many of his patients had had some kind of treatment. Several of his patients with cancer of the breast had complete recession of metastases after bilateral oophorectomy, which is now a recognized form of treatment. A number of uterine and cervical cancers were "cured" by curettage and cauterization.

Rae[20] in 1935 reported the spontaneous regression of a hypernephroma. Rae reviewed the various factors which may be active in spontaneous regression as suggested by Rohdenburg[21] and by Ewing,[4] and estimated that such regressions occurred in one in 100,000 cases. McSwain et al.[15] in 1949 reported the apparent cure of three patients with Ewing's tumor of bone, in one of whom there was disappearance without direct treatment of apparent pulmonary metastasis. Dunphy[3] in 1950 reported a case of spontaneous regression of a pelvic carcinoma proved to be widely disseminated throughout the abdomen. The abdominal masses disappeared spontaneously but nine years later a mass of lymph nodes filled with tumor identical to the original was removed from the inguinal region. At the time of the report there was no evidence of recurrent or metastatic cancer thirteen years after the original inoperable pelvic tumor was discovered and nearly four years after excision of the metastasis in the groin. In 1953 Morton and Morton[17] reported seventeen cases which demonstrated how unpredictable cancer is as a disease. They collected and tabulated thirty patients with malignant melanoma with metastases who were alive and well from six to thirty-six years. Sumner[27] in 1953 reported the case of a pregnant thirty year old woman who had widespread metastases presumably from a malignant melanoma of the skin of the leg. Several of the nodules were excised but many continued to grow until she was delivered of a normal child. Then the masses disappeared, leaving depigmented areas in the skin, and four years after the first visit there were no signs of recurrence or of metastases. In 1955 Allen[1] described a case of malignant melanoma during pregnancy. All tumor nodules disappeared promptly after delivery and there is no sign of melanoma twelve years later. The behavior of the tumor in Sumner's[27] and Allen's[1] cases is very similar and is at complete variance to the course usually taken by melanomas during pregnancy. Levison[14] also has reported the spontaneous regression of a melanoma. His patient was a man who had pulmonary metastases from a malignant melanoma of the choroid. Within six months and without any treatment, the pulmonary nodules disappeared and melanogens disappeared from the urine.

Penner[19] in 1953 reported the spontaneous regression of a case of myosarcoma. In many ways the case is similar to the one we have reported herein. Both patients were infants, the tumor involved soft tissues of the thigh, eroded bone, and some areas of the biopsies were somewhat similar histologically.

Lemon[13] listed eleven cases of "spontaneous" regressions. Two of these patients, however, had been treated with Coley's toxins and two had received x-ray therapy to the primary tumor.

An analysis of the foregoing reports indicates that although complete spontaneous regression of malignant tumors is extremely rare, many cases of partial regression, or regression for long periods of time, have been reported. These cases indicate that some tumors grow in cycles with times of rapid growth alternating with stationary periods or recessions. Such fluctuations of growth are so common that this phenomenon must be kept in mind when evaluating the effects of therapy or in giving a prognosis. When such a spontaneous regression occurs, the doctor is astounded that the usual prognosis was so far wrong, and the patient and family are convinced that a miracle has occurred. If our patient had received x-ray therapy or had been treated with one or more chemotherapeutic agents, certainly such therapy would have been given credit for the cure. Had the baby received injections of "serum" by one of the many cancer "quacks," cure might have been claimed for such "therapy."

POSSIBLE FACTORS CONCERNED IN SPONTANEOUS REGRESSION OF MALIGNANT TUMORS

There are many factors, acting singly or in combination, to produce spontaneous regression of malignant tumors. These may be listed as follows: (1) interference with blood supply; (2) inflammation about borders or in the body of the tumor; (3) toxicity and fever from local

or general infection; (4) heat externally applied; (5) severe general metabolic alterations; (6) alterations of hormonal balance; (7) general or local immunity.

One or a combination of the foregoing conditions may produce changes within or about the tumor, such as hyaline degeneration of blood vessels, mucous degeneration of stroma and parenchyma, and calcification of the parenchyma and capsule.

1. Interference with blood supply: The blood supply to a tumor may be cut off by twisting the pedicle and occluding the nutritive vessels. The nutritive vessels may become thombosed. Hemorrhage into or around a tumor may produce ischemia through pressure.

2. Inflammation about the borders or in the body of the tumor may produce softening and the entire mass may slough out.

3. Toxicity and fever from local or general infection: For many years it has been recognized that an occasional malignant tumor will regress partially or completely following a severe infection such as erysipelas, pneumonia and typhoid fever. William B. Coley developed the bacterial toxin treatment for advanced inoperable malignant tumors. Nauts, Swift and Coley[18] reviewed 484 cases of histologically confirmed malignant disease in which Coley's toxins were used. These included cases of carcinoma, malignant melanoma, bone sarcoma, soft parts sarcoma, lymphosarcoma and Hodgkin's disease. Nauts et al.[18] stated that of 312 inoperable cases there were 190 complete regressions. Such remarkable results in hopeless cases has not been achieved by any other method of treatment. Why then, did Coley's toxin treatment fall into disrepute? They point out that the chief factors leading to the discontinuance of the use of Coley's toxins were: (1) the variability of the toxin preparations when made commercially, (2) failure to carry out the optimum technic, (3) the development of equipment and technics of radiation (following heavy x-ray therapy they suppose the toxins are unable to penetrate the tumor), and (4) the widespread use of all kinds of injections by cancer "quacks" helped bring Coley's toxin therapy into disrepute. Nauts et al.[18] conclude that the results obtained from the use of Coley's toxins justify further research and clinical trial of the method.

4. Heat externally applied: Rohdenburg[21] stated that some of the cases of "spontaneous regression" of cancer of the cervix and uterus he had collected had followed curettage and cauterization. Such cases should not be considered "spontaneous regressions" because it is entirely possible that such cauterization could destroy the entire cancer. Rohdenburg[21] points out, however, that in the transplantation of animal tumors the application of even low degrees of heat to the animal tumors decreases the percentage of "takes."

5. Severe general metabolic alterations: It has long been recognized that malignant tumors may regress when there have been profound alterations in the general metabolic state. Tumor grafts do not take well in animals in poor nutrition and having certain vitamin deficiencies. Therefore in some patients with rapidly growing malignant tumors the growth may recede when the patient becomes profoundly cachectic.

6. Alterations of hormonal balance: During the past ten years a great deal has been learned about the influences of hormones on certain malignant tumors. The beneficial effect of stilbestrol in cancer of the prostate is well established. In metastatic cancer of the breast the value of bilateral oophorectomy and the use of androgens and estrogens have been proved to be of value in a high percentage of cases. Bilateral adrenalectomy or hypophysectomy provides palliation for some hopeless cases of cancer of the breast which could not have been helped five years ago. Cortisone and metacortin® have also been temporarily effective in certain tumors.

In performing oophorectomies and adrenalectomies one very frequently finds metastases from cancer of the breast in the ovaries and adrenals. One of the authors (L. D.) recently operated upon a patient who had extensive invasion of both ovaries and both adrenals. It would seem entirely possible that in some of the cases reported as "spontaneous regression" of cancer of the breast there was actually destruction of the ovaries and adrenals, or even of the hypophysis by metastatic cancer. One must note, however, that therapeutic effect in the usual case stops short of enduring "cure."

7. General or local immunity: The possibility of local or general immunity to malignant tumors has intrigued the medical profession for generations. Handley[9] stated: "The progress of a cancer is normally accompanied by regressive or curative processes." The frequent

finding of fibrosis and round-cell infiltration in and around certain tumors has caused many pathologists to conclude that these are evidences of a natural resistance against the cancer. The long-dormant period before local recurrences appear in some cases, and the long interval before distant metastases appear in others, indicate some form of natural resistance. Occasionally, cancer will be quiescent for many years and then, following an operation or an illness unrelated to the malignancy, there will be an explosive spread and extremely rapid growth suggesting the sudden breakdown of the natural defences.

In 1906 Gaylord and Clowes[5] noted that there was spontaneous cure of cancer in 23 per cent of inoculated mice. They collected fourteen human cases of "spontaneous cures" and concluded that such cases demonstrated the existence of immune forces capable of terminating the disease.

In 1907 Mackay[16] reported a case of spontaneous regression of advanced metastatic cancer of the breast. He postulated the regression as being due to the building up of specific tumor antibodies.

In 1952 Hauschka[12] reviewed the literature dealing with the immunologic aspects of cancer, listing 220 references. Hauschka stated, "The ambiguities in the data now available are due in large measure to the use of conventional materials, long-propagated neoplasms and unsuitable host stocks." Hauschka concluded, "Eventual demonstration of specific neoplastic antigens appears dubious since the critical results to date have been largely negative."

Graham and Graham[7] expressed the opinion that Hauschka's conclusion based on immunologic work done on animals with transplantable tumors would not apply in human cancer. Graham and Graham listed a number of observations supporting host resistance to certain cancers. They expressed the opinion that the body is capable of some defensive behavior toward certain tumors as shown by the elaboration of specific antibodies. They tested the sera of forty-eight cancer patients for antibodies to their own tumors and found that twelve had measurable titers.

Attempts are being made to induce resistance to cancer. Stone, Curtis and Brewer[24,25] in 1951 outlined the technic and then in 1955 Stone and Schnaufer[26] reported the results. The results in mouse mammary cancer had been very encouraging but all of the subjects with advanced human mammary cancer had died. One subject had lived four years, or longer than had been anticipated.

In the attempt to find an explanation for the rapid regression of our patient's tumor, each of the previously listed factors was considered. As far as could be determined, there was no interference with blood supply or inflammation in or about the tumor to account for the regression. The patient was not severely toxic from a local or general infection. Her temperature never rose above 38.8°c., even after the exploratory operation and biposy. There were no severe metabolic alterations. Since we do not know the origin of this tumor, it is difficult to attribute the regression to the effect of particular hormones. One can, of course, refer to the normal maturation of embryonal structures. We ought, then, to consider the development of a local or general immunity to explain the regression. We can only speculate about the origin and mode of action of such immunity.

THE PROBLEM OF DELAYED RECURRENCE AND LATE METASTASES

Cancer of the breast and cutaneous and ocular melanoma may have latent periods of many years before metastases appear. Willis (Table A) lists the latent periods for some of the more common tumors.

There are reports listing even longer latent periods than those listed in Table A. Hartmann[11] reports a case of cancer of the breast which recurred in the operative scar forty-three years after radical mastectomy. Sklaroff and Sterling[23] report local recurrence thirty-four years after radical mastectomy. They list ten references, one giving a latent period of forty-one and another of forty years.

It is interesting to speculate as to how the cancer cells could remain dormant for ten to forty-three years. What conditions kept the cells dormant and then what released them to resume active growth? Hadfield[8] discussed the dormant cancer cell. He showed that tumors can be kept at −70°c. for as long as five years. When the frozen tissue was warmed and hydrated, it was alive; its cells multiplied and could be transplanted. Hadfield showed that malignant cells can survive long periods of metabolic arrest, even when separated from the parent growth. He believed cancer cells in the operative site become locked up in poorly

vascularized mature connective tissue and may be kept in a state of relative anoxia. Lymph node metastases may be kept relatively anoxic in a similar manner. He believes that the local implants and axillary metastases may be reactivated if the scar is revascularized and adquate oxygen supplied.

Hadfield's article stimulated a series of letters in the *British Medical Journal*. Handley[10] takes exception to Hadfield's[8] explanation of late recurrence. Handley states: "For years tendril-like lines of proliferating cancer cells may push their way through the capillary lymphatic vessels around the primary growth. The choked lymphatics are distended until they rupture, an event which excites a vigorous inflammatory reaction, which as a rule destroys the cancer cells. But, meantime, the advancing microscopic edge of the growth has passed on like an invisible ringworm, often without giving any clinical sign of its presence for years, until it invades one of the serous cavities. When this happens visceral metastases rapidly ring down the curtain." Worrall[30] expressed the opinion that restricted nitrogen balance produces a state of dormancy in the cancer cells. An increase in nitrogen balance leads to increased protein and increased cell growth. A negative nitrogen balance sufficiently prolonged ends in death from loss of protein. Worrall[30] states, "The factors responsible for dormancy of cancer cells in situ as well as for restriction of the growth of normal cells, must therefore be sought in the organism as a whole, particularly with reference to its regulated tendency to nitrogen retention." Ghadially[6] writes that although Handley's hypothesis of lymphatic permeation (quoted heretofore) may explain some cases of delayed secondary growths, it does not account for most late recurrences and he believes that there are dormant cancer cells. Ghadially[6] agrees with Hadfield[8] that such foci must have been implanted before excision of the primary growth. He quotes several experimental studies which showed that a single application of a carcinogen failed to produce tumors in mice; but when these animals were later treated with repeated applications of a non-specific irritant such as croton oil, large numbers of tumors were produced. Ghadially states, "These studies suggested that the initial action in carcinogenesis constitutes a sudden and irreversible process whereby a few normal cells are changed into permanently altered latent tumor cells which lie dormant till stimulated into activity by a promoter such as croton oil. The treatment with croton oil need not follow immediately the single application of carcinogen—successful results can be obtained even when croton oil applications are delayed for months." He believes that these experiments not only confirm the existence of the dormant tumor cell but also suggest how they may be awakened into activity at a later date. He further quotes the experimental evidence concerning the reduction in mitotic rate produced by diet reduction. Ghadially[6] concludes with his experimental evidence concerning the action of cortisone in depressing the epidermal mitotic rate in mice and also inhibiting papilloma production by a potent carcinogen such as 9-10-dimethyl benzanthracene.

There is an extensive literature on the subject of delayed recurrence and late metastases. A few of the explanations have been listed. We have long thought that in certain cases local anoxia could explain the long delay before recurrence. It is usually supposed that dense, avascular fibrous tissue can "lock up" cancer cells in an operative scar, lymph node or even in the lung. When the fibrous tissue is revascularized and adequate oxygen supplied, the cancer cells can become reactivated.

There are many late metastases which cannot be explained on the basis of anoxia from scar tissue alone. The necessity of the presence of one or more chemical compounds before the cancer cells are activated seems a good suggestion. Ghadially[6] lists experimental evidence which shows that certain chemical compounds "set the stage" and that other chemicals "trigger" the process of carcinogenesis or reactivation. This problem is being energetically pursued throughout the world and we have good reason to hope that it may be solved within the next few years.

SUMMARY

1. Malignant tumors frequently show fluctuation in rate of growth. Some have periods of very slow and then rapid growth. Some are slow to metastasize or the metastases may be dormant for many years. There are a few proved cases of malignant tumors that have completely regressed without any therapy.

2. Most of the cases reported as "spontaneous cures" cannot be accepted when examined

critically. To aid in the segregation of cases of complete spontaneous regression, a list of criteria is proposed.

3. A case is reported of a girl who had an extensive fibrosarcoma when five months of age, received no treatment and is now entirely well at thirteen years of age.

4. A list of possible factors concerned in spontaneous regression of malignant tumors is presented.

5. The various theories which have been suggested to explain late recurrence and metastasis are discussed.

6. The variability of rate of growth of all types of malignant tumors must be considered when evaluating a particular type of therapy or in estimating the prognosis.

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DISCUSSION

Carleton Mathewson, Jr. (San Francisco, Calif.): I wish to congratulate Dr. Dobson on his exhaustive study and comprehensive presentation of a most perplexing problem.

No doubt most surgeons as they gain experience have been impressed by the strange and unpredictable behavior of malignant tumors, and many have devoted a good portion of their lives to detailed studies of the problems involved. The long list of possible factors concerned in the spontaneous regression of tumors and the numerous theories which have been suggested to explain late recurrence and metastasis serve only to emphasize our inability at the moment to understand these problems completely. Dr. Dobson's excellent presentation is a timely one, not because he has brought us any nearer to an explanation of the spontaneous regression of malignancies but because he has reemphasized the necessity of careful scrutiny of all the facts involved in the behavior of tumors before any logical conclusions can be drawn.

Unfortunately, unscrupulous "quacks" have capitalized upon their recognition of the unpredictable manner in which tumors respond to treatment; these persons take full credit for the occasional spontaneous regression or temporary arrest of malignant growths. It is equally unfortunate that many responsible physicians have unwittingly based their belief in the efficacy of certain methods of treatment on the same point. I hope that Dr. Dobson's article will serve to reawaken us to this danger.

Perhaps many of us subject our patients to unwarranted procedures on the basis of misinterpretation of experiences of our own and that of others. It is important when considering therapy that we be reminded from time to time of this possibility and that we scrutinize the end before we justify the means. I am reminded of Dr. Eloesser's pertinent remarks on one occasion when he was called upon to discuss this problem. He so rightly said, "It is not important how long you live, but rather how you live." In the light of this remark, it is difficult to justify the recent enthusiasm in certain quarters for many of the surgical procedures which have come to be known as "all-American."

In recent years surgeons and pathologists alike have come to the realization that the tumors of infancy must be considered in an entirely different category than those in adult life. It is well recognized, I believe, that not only is the true nature of tumors in infants difficult to recognize, but also these tumors frequently change their microscopic character and may regress spontaneously. Here the clinician must be particularly careful in his prediction of response to treatment and prognosis.

Unfortunately, it is not often possible to follow the natural course of an untreated tumor except in those who refuse treatment, and as a rule these individuals are unwilling to subject themselves to follow-up examination. Usually the clinician feels compelled to institute some type of treatment even though he has no faith in the possibility of a favorable outcome. If treatment is not undertaken by one, it almost certainly will be by another. Although there are a few authentic cases that meet Dr. Dobson's criteria of spontaneous regression, most have received one type of therapy or another.

In our own Tumor Clinic we have no case of spontaneous regression of a proved malignant tumor that fits Dr. Dobson's strict criteria; however, we do have a fair number that for one reason or another have responded unpredictably well to inadequate therapy and therefore serve to remind us of what we have come to call by Dr. Emile Holman's terminology "the vagaries of carcinoma."

Alfred Strauss (Chicago, Ill.): I am particularly interested in the subject of spontaneous regression of malignant tumors, and it may be of interest to Dr. Dobson to know that just before leaving Chicago this fall, I saw an eighteen year old girl who at the age of one had had a highly malignant sarcoma of the rectum which was so fixed that it was considered inoperable.

The Pediatrics Department decided to give the patient deep x-ray and radium implantations. Following these treatments a very severe infection developed with high temperatures. A good part of the rectum and the anterior wall of the bladder, as well as the posterior wall of the vagina, sloughed away so that involuntary stools and urine poured out of this large perineal opening.

Two years later the Pediatrics Department referred the patient to me to see if something could be done for her. I explored and found no signs of any malignancy; but since there was so much scar tissue and the entire rectum was gone, we decided to perform permanent sigmoid colostomy and implanted both ureters into the sigmoid. Today the young lady is tall, fine looking and normal both mentally and physically. The implantation of the ureters in the colostomy has given her no trouble, but there is a slight bulge of the posterior wall of the bladder at the perineal region. After carefully examining her physically as well as x-raying the gastrointestinal tract, several of us have concluded that this is a case of spontaneous cure produced by x-ray and radium and a very serious infection which followed these treatments.

We have done some experimental work as well as some clinical observation which proves that when carcinoma degenerates and undergoes necrosis, it undergoes spontaneous cure and the end products of this degeneration produce a relative immunity in the patient and absolute immunity in animals. We believe that each individual who has a carcinoma has his own immunity against his own carcinoma, and upon that immunity depends how long the patient lives following any kind of treatment, whether it be surgery, x-ray, radium, electrocoagulation and so forth. We believe the character of the malignancy is one factor, but the natural immunity of the patient is a greater factor. To prove this in animals we can, by the degeneration and regression of tumors, produce an absolute immunity.

1. In January, 1940, we transplanted Brown-Pearce carcinoma into the testicles of a large Belgian hare; the carcinoma grew very rapidly in the testicles and produced generalized carcinomatosis. When some of these tumor cells from the testicles were injected into the skin, a tumor was produced about the size of a walnut within three to five weeks; this tumor then degenerated, regressed and became resorbed. When this took place, all of the original tumor of the testicle, as well as of the metastasis, disappeared and the animal was absolutely immune to further implanta-

tion of carcinoma. This was uniform in a large series of Belgian hares.

2. M. R. Lewis, D. B. Maxwell and P. M. Aptekman took some white rats which originally had carcinoma and transplanted some of this original carcinoma of the rat into a pocket in the skin so it had a poor blood supply. The tumor grew to a certain size and then degenerated and became resorbed. With it all of the original carcinoma of the rat disappeared and the rat was absolutely immune to further implantation. When the implanted tumor in the pocket of skin was excised, the original carcinoma did not disappear and the animal was not immune to implantation. Therefore the important factor is the degeneration and absorption of the transplanted tumor in the pocket of skin.

3. In the report of thirty inoperable cancers treated by Coley's toxin, in which diagnosis was confirmed by microscopic examination, from selected and special studies, the conclusion was reached that by continuous injections for several years these highly malignant tumors were completely cured not only by the degenerative process of the tumor itself which threw antibodies into the circulation but also many of these injections were intramuscular and not in the tumor. This proved that Coley's toxin—which is a mixture of Streptococcus erysipelatis and Bacillus prodigiosus—produces a systemic effect, increasing the resistance and the antibodies in the cancer patient, and produces an absolute cure.

4. We have employed electrocoagulation on human beings. In 1913 we started to do electrocoagulations of carcinoma of the colon but especially those of the rectum. Since that time we have performed about 250 electrocoagulations for carcinoma of the rectum, usually no higher than 5 or 6 inches from the anus and most of them on the posterior or lateral outer wall of the rectum. The results have been excellent; in approximately 75 per cent we have gotten better than a five-year cure, in 30 per cent a ten-year cure, and in 15 per cent a complete cure. Many of these patients died of some other disease, such as coronary or cerebral hemorrhage or pneumonia. In those cases in which we performed autopsies, we found no cancer cells, or if glands were found along the rectum, they evidently were contained as the patient had no symptoms of the disease or the cancer had made no progress in all these years. We believe electrocoagulation not only produces mechanical destruction of the tumor but also causes the throwing off into the circulation of certain substances and antibodies which immunize the patient against further progress of the disease.

5. About fifteen years ago we contended that when a large carcinoma of the stomach or colon was widely resected and some malignant lymph glands were left behind, the removal of this primary large mass permitted the patient's normal resistance to carcinoma to return. We believe that the outpouring metabolic action of such a large carcinomatous mass overwhelms the normal resistance of the patient and, when removed, gives an opportunity for the normal resistance to return, because in the operation a certain amount of absorption and protein reaction is taking place which helps to increase the normal resistance forces the patient has. There are many patients who lived ten, fifteen and twenty years after operations for highly malignant tumors, and on second operations for other conditions such as gallstones no glands could be found; or if they were present, they seemed to be contained and had no effect on the health of the patient or his prognosis.

Recently, in a series of cases Graham and Graham have shown that the titer remarkably increased in cancer patients after removal of the primary carcinomatous mass, which primarily confirms the original clinical observations made by us fifteen years ago.

In conclusion, in our work on Belgian hares we as well as Aptekman and co-workers have shown one common factor, i.e., in animals when tumor transplants undergo necrosis and resorption certain substances are absorbed by the animal which render it immune. This not only destroys all cancer tissue in the animal but also prevents further implantation of malignant tumor tissue into the animal—in other words, it has an absolute immunity.

The cures that have been produced with Coley's toxin and the work we did on electrocoagulation of the rectum show that when a tumor degenerates in a human being, it also produces an immunity. However, that immunity is only relative in some instances, probably due to the quantity and amount of absorption of the necrotic tumor. The same principle of necrosis also holds true in those cases of inoperable carcinoma in which there is intercurrent severe infection which produces sloughing and necrosis of the carcinoma and causes spontaneous cure.

LEONARD DOBSON (closing): I wish to thank both Drs. Mathewson and Strauss for discussing my article. Dr. Strauss covered some of the current research which I did not have time to mention.

In closing, I wish to emphasize the fact that had *any* treatment been used for this child, that treatment would have been given credit for the cure. Had we used x-ray or a chemotherapeutic agent, that therapy would have been given credit. Had the family taken the baby to one of the many cancer "quacks" and the baby had received serum, herbs or a special diet, the case could then have been included in the "quack's" list of testimonials. We must therefore consider the fluctuation in growth of malignant tumors whenever we assess the effect of any type of therapy.

Autotransplantation of the Adrenal Cortex to the Mesentery Combined with Adrenalectomy and Oophorectomy in the Treatment of Metastatic Carcinoma of the Breast

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MORE than fifty years have passed since Beatson[1] and Lett[2] demonstrated that women with metastatic carcinoma of the breast could derive benefit from surgical castration. Since that time there have been numerous reports on medical methods of inducing remissions in cancer of the breast by disruption of hormonal balance, i.e., the administration of testosterone, estrogen or cortisone. Huggins and co-worker[3] showed that certain cases of metastatic carcinoma of the breast were improved following oophorectomy combined with adrenalectomy, and suggested that such remissions were due to the total removal of endogenous estrogens.

It is the purpose of this article to report still another method of hormonal disruption in the treatment of eighteen patients with metastatic carcinoma of the breast, and to describe the experimental and theoretic considerations that led to its establishment.

EXPERIMENTAL CONSIDERATIONS

It has been demonstrated that the liver inactivates natural and synthetic estrogens and androgens.[4–6] However, essential adrenal corticoids may not be completely inactivated by the liver since certain life processes can continue in the adrenalectomized rat when an adrenal gland is transplanted to the portal circulation.[7–11] There is experimental evidence that the adrenal cortex can produce sex hormones.[12] It is assumed that the adrenal estrogens and androgens can be metabolized by the liver in the same manner as the gonadal steroids. Thus if the adrenal cortex is transplanted into the portal circulation, its estrogens and androgens could be inactivated by the liver without complete inactivation of essential cortical steroids. In the rat the growth of certain hormone-dependent gonadal tumors[13] is influenced by the presence or absence of the adrenal glands.[14] Concurrent studies by us suggest that the cancer-promoting secretions of the adrenals may either be inactivated by the liver or modified to an inhibiting form.

Grayhack and Harris[15] showed that dogs remain in a relatively normal state when the venous blood of the adrenal is shunted by anastomosis through the portal circulation. Following these experiments the same authors performed operations shunting the adrenal venous blood on five patients with metastatic carcinoma of the prostate, but to date the results have not been reported. Galante et al.[16] performed similar adrenosplenic shunts on four women with metastatic carcinoma of the breast. One of their cases, evaluated after 190 days, in which there was no detectable urinary estrogen, showed a rise in urinary 17-hydroxycorticoids after the administration

of ACTH. In each group of patients it would be of extreme importance to know the status of the anastomoses as demonstrated by injection methods at autopsy.

Current experiments on dogs performed by us in conjunction with Sanford Leeds, M.D., have confirmed the results of our earlier trials concerning the technical difficulties involved in the attainment of a patent anastomosis between the adrenal veins and the portal veins. The difficulties encountered were thrombosis, incomplete ablation of by-passing accessory adrenal veins, and the inability to prevent the development of new venous channels postoperatively, as shown by the injection of a radiopaque mass into the vascular tree. We decided, therefore, to autograft portions of the adrenal cortex into the mesentery of the small bowel at the time of bilateral adrenalectomy.

In summary, the adrenal cortex was grafted into the portal circulation, in addition to adrenalectomy and oophorectomy, to achieve: (1) the intraportal passage of adrenal secretions with the least likelihood of circumvention of the liver, (2) the theoretic negation of adrenal sex hormones which could stimulate cancer of the breast, (3) the autogenous contribution of life-supporting cortical steroids, and (4) the inactivation or modification of adrenal cortical steroids other than gonadal, which may stimulate the malignancy.

CLINICAL STUDY

Preoperative Preparation. The first patients were prepared by administration of intramuscular cortisone, desoxycorticosterone and oral salt, and then with a slightly modified form of the treatment recommended by Huggins and Bergenstal.[17] The later patients have received no premedication; steroid administration is started when the patient is on the operating table. One liter of 5 per cent glucose in water, containing 100 mg. of hydrocortisone, is administered intravenously through a vein in the foot. During induction of anesthesia 250 cc. of this hydrocortisone solution are exhibited rapidly by vein; the patient's blood pressure is kept close to preoperative levels by varying the number of drops per minute. By the end of the operation 400 to 600 cc. of fluid containing 40 to 60 mg. have been given as well as whole blood as needed. In the first twenty-four hours an approximate total of 100 to 200 mg. of hydrocortisone has been administered. For the next two days it may be necessary to continue the administration of the intravenous hydrocortisone solution; the amount of steroid used will depend upon the patient's needs.

Surgical Procedure. It is now deemed advisable that whenever feasible the operation be performed in one stage, through a single high transverse abdominal incision. This procedure obviates repeated operations and the serious shock that often ensues from frequent changes in the patient's position. After the abdominal exploration the ovaries are removed. The right adrenal gland is approached first, since its extirpation may offer the greater difficulty. After removal of this gland it is aseptically freed of fat and connective tissue. It is then transected to expose the medulla, which together with some of the brown zone of reticularis is removed by a scalpel. The remaining cortex is thoroughly rinsed in saline at room temperature and is sectioned into 1 cm. square pieces. Each gland should provide eight to fifteen such segments, providing there is no obvious gross carcinomatous infiltration. When the latter is encountered, as it was in seven of the cases, no adrenal tissue within 1 cm. of a visible metastasis is used. The grafts are inserted into pockets made in the mesentery of the small bowel adjacent to the bowel wall, and anchored and identified by closing the pocket with a single silk suture. Ten to fifteen minutes are required from the time of removal of the gland to the insertion of its grafts into the mesentery. The left gland is then removed; and if the patient's condition permits, the gland is similarly transplanted. Portions of each gland are retained for histologic examination.

Postoperative Care. The immediate postoperative care of these patients follows the same pattern of treatment as that used for simple adrenalectomy and has been described in detail by Huggins and Bergenstal.[17] In addition, immediately after operation ACTH is administered because it may possibly stimulate the growth of the grafts. The program followed for ACTH administration is 40 μ of the gel two times daily for one week, 40 μ daily for two weeks, 40 μ on alternate days for two weeks, 20 μ on alternate days for two weeks, and 20 μ one to two times weekly for the subsequent three to five weeks. By the time ACTH is discontinued, the patients are maintained on

TABLE I

SUMMARY OF CASES

Patient and Age	Previous Therapy	Menses	Preoperative Status	Date of Operation	Postoperative Medication	Duration of Subjective Improvement	Criteria of Objective Improvement	Survival (days)
I. K., 39	Radical mastectomy, 1951	Active	Metastases in bones; severe pain in hip	March, 1953	10–15 mg. cortisone/day; 2 mg. DCA/day	16 mo.	X-ray regression of lesions in bones for 1 yr., then activation	769
J. H., 49	Radical mastectomy, 1950; course of testosterone	Surgical castration, 1950	Pleural effusion; metastases in bones	September, 1953	37.5 mg. cortisone/day; 2 mg. DCA/day	Continues	X-ray regression of lesions in bones; no recurrence of pleural effusion	Alive
M. H., 50	Radical mastectomy, 1952	Active	Pulmonary metastases; pleural effusion	December, 1953	10–15 mg. hydrocortisone/day; 2 mg. DCA every 3rd day	Continues	No recurrence of pleural effusion or x-ray evidence of disease; 23 lb. gain in weight	Alive
R. L., 46	Radical mastectomy, 1951; course of testosterone	X-ray castration, 1951	Multiple pulmonary metastases	December, 1953	20–30 mg. hydrocortisone/day; 25 mg. desoxycorticosterone trimethylacetate/mo. (last 2 mo)	15 mo.	Marked x-ray regression of pulmonary lesions for 14 mo., then activation; 16 lb. gain in weight	498
D. B., 44	Radical mastectomy, 1952	Active	Metastases in bones; marked, multiple metastases in liver seen at surgery	December, 1953	5–15 mg. hydrocortisone/day	Continues	No change in lesions by X-ray; 19 lb. gain in weight	Alive
H. McD., 61	Radical mastectomy "many years ago"	Ceased "many years ago"	Metastases to lungs, bones, and spinal cord with paraplegia and loss of bowel and bladder control	February, 1954	45 mg. hydrocortisone/day	9 mo.	Regained bowel and bladder control and some movement of extremities; terminal exacerbation all lesions	421
F. M., 71	Radical mastectomy, 1929; course of estrogen and of testosterone	Ceased, 1939	Metastases in bones	March, 1954	20 mg. hydrocortisone/day	1 yr.	X-rays showed slow progression of lesions in bones	670
E. G., 52	Radical mastectomy, 1947; course of testosterone and cortisone	Surgical castration	Metastases in bones and soft tissue	April, 1954	75 mg. cortisone/day	None	None	45
H. S., 51	Radical mastectomy, 1949	Ceased, 1953	Metastases in bones and soft tissue with ascites	June, 1954	50–100 mg. cortisone/day; 2 mg. DCA/day	6 mo.	Disappearance of ascites; regression of lymph nodes and opposite breast tumor for 6 mo.	237
I. F., 34	Radical mastectomy, 1953	Active	Metastases in bones	June, 1954	5–50 mg. cortisone/day	4 mo.	X-ray regression of lesions in bones at 3 mo., then marked exacerbation	242
S. R., 50	Radical mastectomy, 1951	Ceased, 1951	Metastases in bones and soft tissue	September, 1954	50–75 mg. cortisone/day and DCA 1–2 mg./day; now on metacorten 17.5 mg./day	Continues	Regression of metastases of skin; x-rays show progression of lesions in bones	Alive
E. B., 50	No previous treatment; inoperable lesion	Ceased, 1946	Retracted, fixed left breast with large regional lymph nodes	September, 1954	20 mg. hydrocortisone/day; 25 mg. desoxycorticosterone trimethylacetate/month	Continues	Decrease in size of primary lesion and regression of regional lymph nodes	Alive

TABLE 1 (*Continued*)

Patient and Age	Previous Therapy	Menses	Preoperative Status	Date of Operation	Postoperative Medication	Duration of Subjective Improvement	Criteria of Objective Improvement	Survival (days)
A. H., 41	Radical mastectomy, 1952	X-ray castration, 1952	Metastases in bones with severe pain	October, 1954	10–15 mg. hydrocortisone/day; 25 mg. desoxycorticosterone trimethylacetate/mo.	9 mo.	X-ray regression of lesion in bone at 4 mo.; exacerbation at 8 mo.	329
M. M., 40	Radical mastectomy, 1949	Ceased 3 mo. before surgery	Massive thoracic soft tissue infiltration	November, 1954	25–37.5 mg. cortisone/day	None	None	98
P. S., 27	Radical mastectomy, 1952; courses of testosterone, radiation, intrathoracic radioactive gold, and cortisone	Surgical castration, 1953	Tissue metastases, including lungs and pericardium	November, 1954	20–30 mg. hydrocortisone/day	None	None	146
A. McG., 62	Radical mastectomy, 1938; courses of testosterone, estrogen, intrathoracic thiotepa	Ceased "many years ago"	Pulmonary metastases with pleural effusion	June, 1955	15–30 mg. hydrocortisone/day	None	None	92

an average of from 15 to 30 mg. of oral hydrocortisone or 25 to 37.5 mg. of oral cortisone daily. There are periods when the requirements increase due to a variety of clinical conditions.

Sodium chloride as enteric tablets is given in doses of 1 gm. three times daily after the tenth day. In some of the patients a persistently low serum sodium level may be restored to normal by an injection of 15 to 25 mg. of desoxycorticosterone trimethylacetate once a month.

In three early cases in which operation was from a lumbar approach, shock was encountered and L-arterenol was employed. One patient required 50 to 70 drops per minute of a 20 μg./cc. solution for a period of two days to maintain blood pressure. Since the adoption of the transabdominal approach, the administration of whole blood and of intravenous hydrocortisone, no further instances of shock have been encountered.

Partial renal shutdown presented a temporary problem in only two of the patients, both of whom recovered by careful control of electrolyte and fluid balance.

In most of the patients a paralytic ileus was observed on the fourth postoperative day. This, too, resolved in from one to three days; and although pituitrin® or prostigmine® had been administered during this period, it is doubtful if they were of significant benefit. Usually by the sixth day medication and light feedings are given orally.

The total daily intravenous fluid for the first three days ranges from 2,000 to 3,000 cc., of which 1,000 to 1,500 cc. is saline. On the third day an ampul containing KCl 1.8 gm., $MgCl_2$ 0.5 gm., and $CaCl_2$ 0.6 gm. is also administered since hypokalemia may be evident at this time.

By complying with these instructions, the procedure has been carried out without difficulty by several competent teams of surgeon and internist. (Table 1.)

CASE REPORTS

Patient I. K. A thirty-nine year old woman had undergone radical mastectomy two years earlier; still menstruated regularly and had extensive bony metastases. An attempt at testosterone therapy was discontinued because of severe nausea. She was operated upon in March, 1953; excellent remission followed, with radiologic evidence of disappearance of bony lesions. She returned to active life and her regular employment. Her steroid maintenance requirements varied between 10 to 15 mg. of cortisone daily. Sixteen months after operation she sustained a pathologic fracture

of the femur, and x-ray demonstrated recurrence of old and the presence of new lesions in bones. Plasma corticoid response to intravenous ACTH demonstrated a 10 μg. rise in 1.5 hours. The patient died May 1, 1955. Her maintenance therapy during the last year of life had increased to 25 to 37.5 mg. cortisone and 2 mg. DCA daily. At autopsy, five of eight adrenal cortical grafts were recovered, the total weight of which was approximately 2 gm.

Patient J. H. A forty-nine year old woman had undergone radical mastectomy three years earlier, followed with surgical castration and a course of testosterone therapy. She entered the hospital with symptoms of bony metastases and pleural effusion. She was operated upon in September, 1953; this was followed with an excellent remission clinically and by x-ray. Her maintenance therapy consists of 37.5 mg. cortisone and 2 mg. DCA daily. Her plasma corticoid response to intravenous ACTH showed a 5 μg. rise in 1.5 hours.

Patient M. H. A fifty year old woman had undergone radical mastectomy one year earlier; she was still menstruating regularly and had soft tissue metastases with pleural effusion and severe dyspnea. She was operated upon in December, 1953, and had an excellent remission which persists. Since operation she sustained a pulmonary embolus and then a myocardial infarction, the former ten days postoperatively and the latter after several weeks. At present there is no radiologic evidence of activity; she has gained 23 pounds and is being maintained on 10 to 15 mg. hydrocortisone daily. Plasma corticoid response to intravenous ACTH showed a 12 μg. rise in fifteen minutes. A repeat intravenous ACTH test after a six-week interval resulted in collapse from anaphylactic shock, from which the patient recovered. She had a long history of hay fever and angioneurotic edema.

Patient R. L. A forty-six year old woman had undergone radical mastectomy two years earlier, followed with x-ray castration. She had an intensive course of testosterone therapy, during which several large metastatic lesions developed in both lungs. She was operated upon in December, 1953, with a dramatic remission until April, 1955. During this time her pulmonary lesions disappeared completely by x-ray and she gained 16 pounds. She required from 20 to 30 mg. hydrocortisone daily for control and also received 25 mg. desoxycorticosterone trimethylacetate per month for the last two months. This patient had a four-year history of ulcerative colitis with diagnostic radiologic findings. Of incidental interest is the fact that her operation did not influence the course of the colitis. In March, 1955, exacerbation of pulmonary metastatic lesions recurred which did not respond to testosterone or a course of triethylene thiophosphoramide. Her plasma corticoid response to intravenous ACTH showed an 8 μg. rise in thirty minutes. She died on April 29, 1955; permission for autopsy was not granted.

Patient D. B. A forty-four year old woman had undergone a radical mastectomy one year earlier; she was still menstruating and had bony metastases. She was operated upon in December, 1953, and massive infiltration of the liver was revealed. She has had excellent remission with no x-ray evidence of progression and a 19 pound weight gain. She has been maintained on 5 to 15 mg. hydrocortisone daily. Plasma corticoid response to intravenous ACTH was negative.

Patient H. McD. A sixty-one year old woman had advanced metastatic cancer of the breast with multiple metastases to lungs, bones and spinal cord which resulted in paraplegia with loss of bowel and bladder control. The radical mastectomy had been performed many years before entry. The patient was operated upon February 22, 1954. A few months after operation, while in a nursing home, she was maintained on 5 mg. and later 45 mg. of hydrocortisone daily. After surgery bowel and bladder control returned, as did sensation in her lower extremities. She also could move her legs but was never quite able to get out of bed. In November, 1954, she began complaining of pain in the back and was rehospitalized. X-rays demonstrated " . . . innumerable areas of bone destruction and collapse, more than on previous examination on February 21, 1954. However, at many areas, there is the appearance of calcification and reossification." Autopsy on April 19, 1955, showed only one small 2 mm. graft. This patient had been operated upon and cared for in an adjacent community. At the time of autopsy it was revealed that of the twelve grafts placed, four in each of three pockets at the root of the mesentery rather than adjacent to the bowel wall, only one small zone of cortical tissue could be demonstrated.

Patient F. M. A seventy-one year old woman had undergone radical mastectomy twenty-five years earlier. There had been no menstrual periods for at least fifteen years. Courses of estrogen and then testosterone did not change the metastases in the bones. The patient was operated upon in March, 1954. There had been a distinct subjective remission. However, after one year x-rays showed new areas of activity in bone in spite of healing replacement of many earlier lesions. There was a period of two months during which she did not require hydrocortisone, but eventually she was maintained on a daily dosage of 20 mg. Her plasma corticoid

response to intravenous ACTH administration was negative. She died 670 days after operation. At autopsy many scattered small metastases were found, as well as terminal congestive failure. All nine of the grafts had taken and weighed approximately 2 gm. The gross appearance of the grafts is shown in Figure 1.

Patient E. G. A fifty-two year old woman had undergone radical mastectomy and surgical castration seven years earlier; she had temporary remissions on testosterone, and then on cortisone, each lasting for approximately one year. Operation was performed in April, 1954, at which time the mesentery was seen to be approximately 2.5 cm. thick due to carcinomatous infiltration. Five adrenal grafts, in which metastic tumor was seen grossly, were implanted. This patient died forty-five days later from mechanical bowel obstruction. At autopsy four of five grafts had taken; the total weight was less than 1 gm. It is significant that grafts "took" in spite of pretreatment for one year with 50 to 100 mg. of cortisone daily.

Patient H. S. A fifty-one year old woman had undergone radical mastectomy at the age of forty-six and had had spontaneous cessation of menses at the age of fifty. She had metastases to bone and soft tissue. The operation was performed in June, 1954. Although the patient died 242 days after operation, there was transient improvement which consisted of weight gain, disappearance of ascites and regression of metastatic lymph nodes and of the tumor in the other breast. She required maintenance of 50 to 100 mg. cortisone and 2 mg. DCA daily. Plasma corticoid response test the day before death showed a 17 μg. rise in 1.5 hours. At autopsy, six of fifteen grafts were recovered and the weight approximated 2 gm.

Patient I. F. A thirty-four year old woman had undergone radical mastectomy one year earlier. She was menstruating regularly. She received x-ray therapy to metastases in her hip. The operation was performed in June, 1954. There was excellent remission with some radiologic evidence of healing, and the patient returned to work. Starting eight weeks postoperatively, she required 5 mg. cortisone daily. However, with exacerbation of a bone lesion two months later and the appearance of a tremendous increase in hepatic metastases, her requirements increased to 25 to 50 mg. cortisone daily. A plasma corticoid response test to intravenous ACTH was negative. The patient died seven months after operation. At autopsy, five of thirteen grafts were recovered, the combined weight of which was about 1 gm.

Patient S. R. A fifty year old woman had undergone left radical mastectomy on May 29, 1951. In 1954 her right breast became red and indurated due to metastases or a new primary carcinoma. Four months prior to operation she noted metastases to the skin of the right breast; an intensive trial of testosterone was ineffective. Operation was performed elsewhere on September 22, 1954. Metastases were demonstrated in the skin, neck, ovaries and bones. Postoperatively the patient felt best when receiving 50 to 75 mg. cortisone and DCA 1 to 2 mg. daily. A survey for metastases on January 19, 1955, showed "extensive osteoblastic metastases in the thoracolumbar spine, pelvis and femur." The patient is now supported on metacorten 17.5 mg. per day. Blood corticoid levels showed no response to intravenous ACTH administration.

FIG. 1. Patient F. M. (A56–9, 670 days). The segment of ileum and its mesentery show that the grafts are present as small nodules close to the bowel wall.

Patient E. B. A fifty year old woman entered the hospital with a red, indurated lesion which retracted the left breast with fixation to the chest wall. There were many large, hard, regional axillary lymph nodes, and biopsy of the latter revealed adenocarcinoma, metastatic from the breast. The patient had not been treated for this condition. This was the only patient in the series who did not have far advanced, widespread disease. Spontaneous cessation of menses had occurred eight years earlier. Operation was performed in September, 1954. An 8 pound weight gain, some regression of the breast mass with mobility of the breast and marked regression of the regional nodes were noted four months after the operation. Her maintenance therapy consists of 20 mg. hydrocortisone daily, and 25 mg. desoxycorticosterone trimethylacetate once a month. Her plasma corticoid response to intravenous ACTH was negative five months after the operation.

TABLE II

SUMMARY OF CASES IN WHICH AUTOPSY WAS PERFORMED

Patient	No. of Grafts Transplanted	No. of Grafts Recovered at Autopsy	Age of Grafts (days)	Estimated Weight of Grafts (gm.)	Plasma Corticoid* Response to Intravenous ACTH
E. G.	5	4	45	1	Not performed
A. McG.	25	24	92	3	Not performed
M. M.	18	17	98	2	Positive
P. S.	15	11	146	2	Not performed
H. S.	15	6	237	2	Positive
I. F.	13	5	242	1	Negative
H. McD.	12	1	421	0.1	Not performed
F. M.	9	9	670	2	Negative
I. K.	8	5	769	2	Positive

* Plasma corticoids were measured by a modification of the Silber-Porter method.[18]

Patient A. H. A forty-one year old woman had undergone radical mastectomy and radiation castration two years earlier. She presented herself with widespread metastases in the bones and had severe pain. Operation was performed in October, 1954. Roentgenograms four months later showed calcification of bone lesions and no progression of the metastases. There has been a distinct reduction in pain. At the end of five months her plasma corticoid response to intravenous ACTH revealed a 16 μg. rise. Her maintenance requirements have been 10 to 15 mg. hydrocortisone daily and desoxycorticosterone trimethylacetate 25 mg. once a month. However, nine months after operation there was exacerbation of lesions in the bones by x-ray examination; in July, 1955, radiation therapy was given to the right hip. This patient died elsewhere on August 28, 1955. Autopsy was not done. During the ten months after operation there had been definite diminution of pain in the involved bones.

Patient M. M. A forty year old woman had undergone radical mastectomy five years earlier, followed with extensive radiation therapy and large doses of testosterone for the past year. Menstruation had ceased three months before admission. The operation was performed in November, 1954. This patient had massive infiltration of the carcinoma starting from the original operative scar and extending over the chest, shoulder and into the neck of such extent that her head was twisted and firmly held. Ninety-eight days postoperatively she died from inanition and extension of the tumor into the upper respiratory passages. There had been no improvement in her condition. Her maintenance therapy was 25 to 37.5 mg. cortisone daily. The day before death her plasma corticoid response to intravenous ACTH was 24 μg. in fifteen minutes. At autopsy, seventeen of eighteen grafts were recovered, the combined approximate weight of which was 2 gm.

Patient P. S. A twenty-seven year old woman had undergone radical mastectomy two years before her original entry, followed one year later by castration and then courses of testosterone, radiation, intrathoracic radioactive gold, and cortisone. She was admitted with extensive soft tissue metastases, with pleural and pericardial effusion. Operation was performed in November, 1954. She died five months later. There had been no clinical improvement. She had been maintained on 20 to 30 mg. hydrocortisone. The plasma corticoids were not measured. At autopsy, eleven of fifteen grafts were recovered, the combined weight of which approximated 2 gm.

Patient A. McG. A sixty-two year old woman had undergone radical mastectomy seventeen years earlier. Pulmonary metastatic lesions were first observed in March, 1955, and they rapidly progressed in spite of androgen and estrogen administration. Pleural effusion in the right side was unresponsive to intracavitary triethylene thiophosphoramide. Operation was performed on June 1, 1955. Postoperatively she was maintained on 15 to 30 mg. hydrocortisone daily. There was no evidence of improvement. Radioactive chromium phosphate and frequent intrathoracic triethylene thiophosphoramide failed to control pleural effusion. The patient died on September 15, 1955. At autopsy, twenty-four of twenty-five grafts were viable and the approximate weight was 3 gm.

Patients A. N. and R. R. These two patients were debilitated and in the terminal stage with extensive metastases; death occurred within twenty-four hours after the operation. (Table II.)

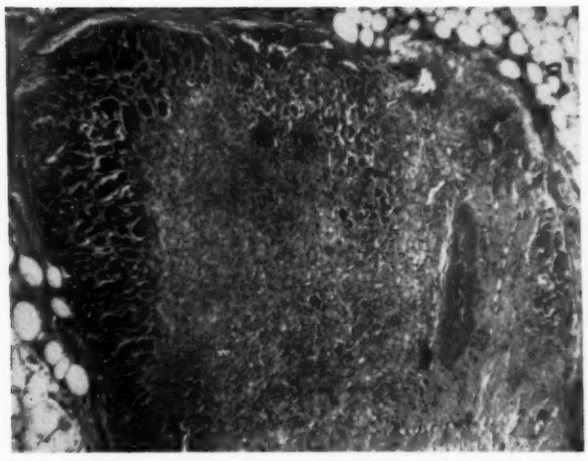

FIG. 2. Patient E. G. (A54–126, 45 days). A cross section of a graft reveals its relationship to adjacent fat and fibrous tissue. A peripheral zone of cords of hyperchromatic cells is distinct from a central zone of pale cells and necrotic material. Original magnification, × 30.

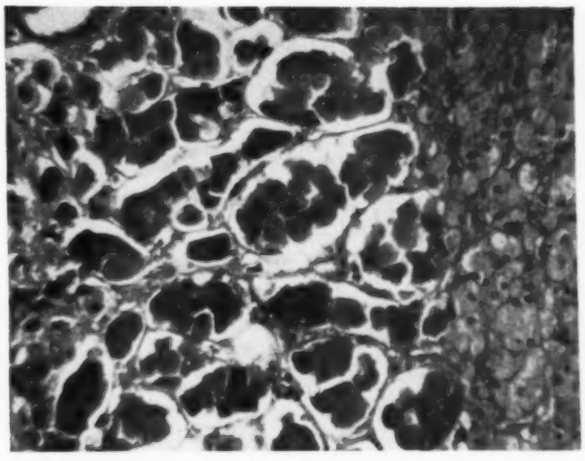

FIG. 3. Patient E. G. (A54–126, 45 days). The cords of hyperchromatic cells take on the arrangement usually noted in the adrenal cortex and probably represent the regenerating elements. The pale cells may be degenerating cells of the transplant. Original magnification, × 100.

HISTOPATHOLOGICAL FINDINGS

Patient E. G. (A54–126, forty-five days.) The transplants were surrounded by fat and a thin rim of compressed fibrous tissue. (Fig. 2.) The outermost layer of large cortical cells was present in the form of short cords. These cells had a deep eosinophilic granular cytoplasm and a somewhat shrunken basophilic nucleus. The clusters of cells were arranged in parallel cords in thin fibrous strands, between which were distinct vascular channels. The innermost portion of this hyperchromatic layer showed some loss of demarcation of the cell groups and degeneration of single cells. There was rather a sharp change to sheets of large cells with a lightly stained vacuolated cytoplasm and a round or oval vesicular nucleus. (Fig. 3.) There was no distinct pattern or arrangement of these cells. The fibrous stroma was extremely scant and there was moderate vascular proliferation. Occasional lymphocytes were present. A thin rim of granular necrotic material remained in some regions, generally in the center of the transplanted tissue surrounded by the lightly stained cortical cells. In other regions the degenerating tissue was surrounded by loose fibrous tissue, and in some places this fibrous tissue replaced the necrotic degenerating elements. Metastatic carcinoma from the breast could be found close to the transplanted tissue.

Patient A. McG. (A55–194, ninety-two days.) The transplanted adrenal cortical tissue was readily recognized by the retention of its general outline. Most of this tissue was undergoing necrosis with the formation of fatty crystals and associated zones of organization of the inflammatory process. In many places the cortical cells that remained had become swollen and revealed a fatty vacuolated cytoplasm and a pyknotic nucleus. There was a beginning encapsulation of the transplanted mass by these strands of fibrous tissue. New regenerating tissue was arising from what had been zona glomerulosa and these cords of cells spread into the degenerated remnants of the transplants. These cells were large with a prominent granular eosinophilic cytoplasm and an oval vesicular nucleus. The cells were present in the form of cords of small clusters and suggested the usual pattern of the zona fasciculata. (Fig. 4.) Some large hyperchromatic vesicular nuclei were present but mitotic figures could not be found. Binucleated cells were not uncommon.

Patient M. M. (A55–40, ninety-eight days.) Most of the transplants showed considerable necrosis and fibrous replacement. There was some regenerating cortical tissue in the form of fairly typical cords of cells. (Fig. 5.) These were present in the outer surface of the transplant and were separated from the mesenteric fat by a thin band of fibrous stroma. The individual cells were quite regular in size and shape. They appeared to have retracted from the basement membrane. The inner portions of the transplanted tissue often contained fibrous tissue and large vacuolated cells with a small, almost pyknotic nucleus. Rarely in the necrotic zone there were fat spaces, both round and needle-shaped, with minimal foreign body reaction.

Patient P. S. (3171, 146 days.) The transplants were fairly well demarcated by an outer boundary

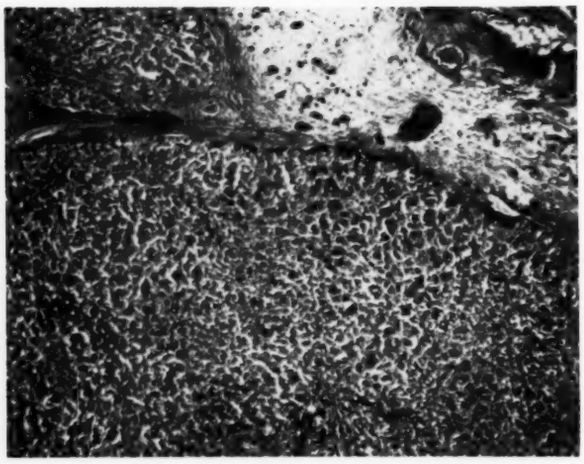

FIG. 4. Patient A. McG. (A55–194, 92 days). A zone of active regeneration is characterized by cords of cells which have replaced the original transplant. Original magnification, × 30.

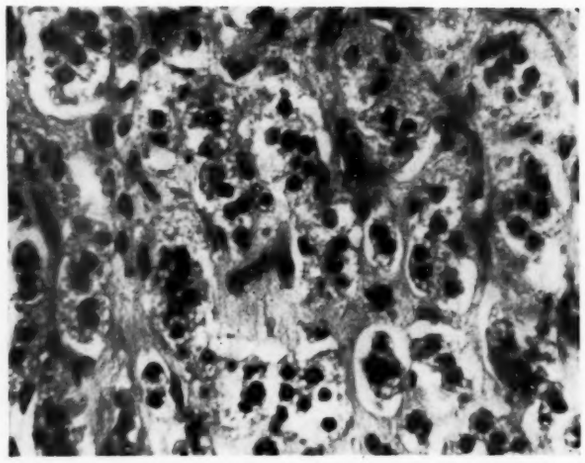

FIG. 5. Patient M. M. (A55–40, 98 days). The regenerated cells are aligned in cords as ordinarily noted in the zona fasciculata. Original magnification, × 100.

of fibrous tissue. Resting against this and extending inward in a moderately nodular pattern were cords of prominent, fairly large cortical cells. These short cords terminated abruptly and the innermost portion of the transplant was composed of sheets of large polyhedral cells pierced by many blood vessels. In the center of the transplant there was usually a distinct necrotic zone which contained fat and was demarcated by a very loose fibrous stroma. The outermost cords of cells, arranged in the typical manner, appeared to be progressing into the sheets of large cells and probably replaced them.

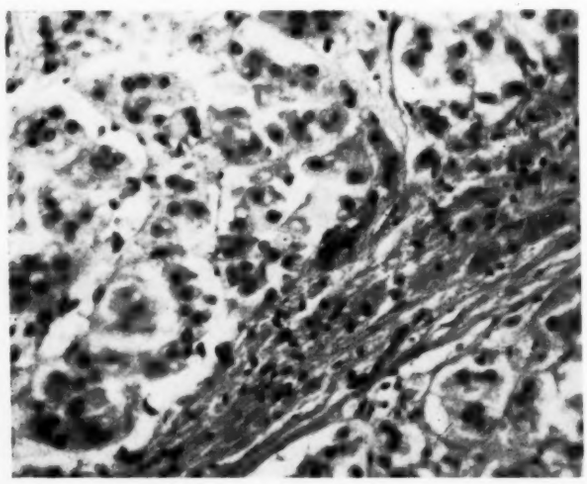

FIG. 6. Patient F. M. (A56–9, 670 days). A band of fibrous tissue produces a nodular pattern by separating the regenerated cells into distinct clusters. The cortical cells are bordered by endothelial channels. Original magnification, × 100.

Patient I. F. (A55–23, 237 days.) The transplants were relatively small and composed of rather distorted cords of adrenal cortical cells which were limited by an outer boundary of fairly prominent fibrous stroma. These cords of cells terminated fairly abruptly where they met the sheets of large polyhedral cells. One or two minute foci of necrosis still remained but generally zones were found which consisted of fibrous tissue.

Patient H. S. (A55–26, 242 days.) The transplants were represented by small foci of fairly typical cords of adrenal cortical cells, surrounded by a variable amount of fibrous tissue. A few small zones of necrotic fatty material remained and these were surrounded by fibrous tissue, scant cortical tissue and some infiltrating neoplastic tissue. Where present, the cortical elements showed a fairly typical pattern, reproducing the normal adrenal cortex. There were also some sheets of large vacuolated polyhedral cells which apparently had not undergone organization or formation of typical adrenal cortex.

Patient H. McD. (3471, 421 days.) A minute transplant could be found surrounded by dense scar tissue in which there were granulomatous foreign body foci. The cells did not show the typical arrangement into cords or fascicles, but were present as sheets of large polyhedral elements. Wrinkled laminated layers of fibrous stroma were associated with these sheets of cells and probably represented scar formation following the degeneration of most of the transplanted tissue.

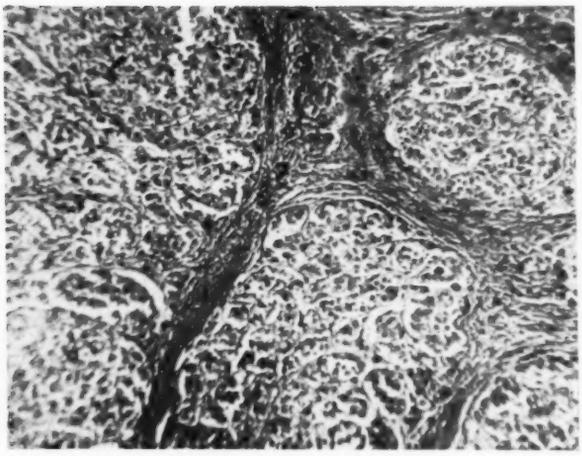

FIG. 7. Patient I. K. (A55–97, 769 days). The nodular pattern is shown. Original magnification, × 60.

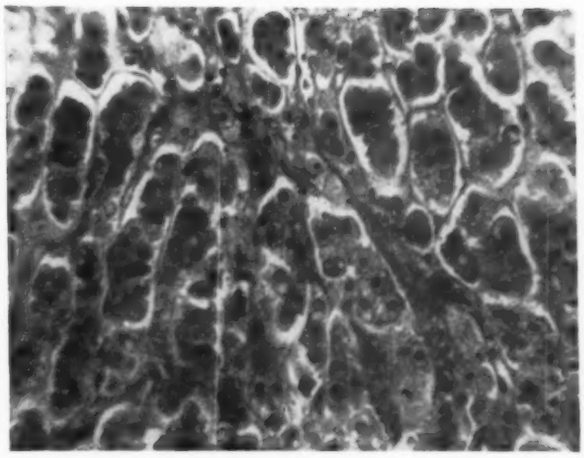

FIG. 8. Patient I. K. (A55–97, 769 days). The cords of cells in the nodules are closely arranged and separated by thin, often collapsed, endothelial channels. Original magnification, × 100.

Patient F. M. (A56–9, 670 days.) The large transplants showed an outer thick border of fibrous tissue. The cords of cells were usually arranged in rather small nodular masses isolated by thin strands of fibrous tissue derived from the outer fibrous bands. (Fig. 6.) The cells were the large polyhedral type with a deep esoinophilic cytoplasm and moderate variation in nuclear size. An occasional giant form was noted. Rarely a minute zone of necrotic original transplanted tissue surrounded by loose scar tissue could be found. The general pattern was highly suggestive of nodular hyperplasia of the adrenal cortex. Some of the large cells showed a condensation of fine granules along the cell membrane and a looser vacuolated cytoplasmic pattern in the central portions of the cells. In some of the regenerating transplants small clusters of metastatic tumor cells had grown into them, but did not appear to alter the growth of the transplant.

Patient I. K. (A55–97, 769 days.) The transplants were characterized by sharply defined nodular masses of adrenal cortical tissue with a peripheral delimitation by bands of fibrous tissue. (Fig. 7.) The nodules were made up of cords of characteristic cells of the adrenal cortex. Between these cords were many thin vascular channels. (Fig. 8.) The cells were polyhedral, fairly uniform in size and shape, and had a round or slightly oval nucleus. The cytoplasm was vacuolated. A very rare enlarged cell was present. Mitotic figures could not be found. The striking features were the formation of distinct nodules, the degree of uniformity of the cells in the nodules, and the resemblance of the cords of cells to normal adrenal cortex in some regions and hyperplastic nodular formations in other areas. There was a slight suggestion of the formation of the zona glomerulosa at the outer border of the cell masses with the remainder of the nodules composed of cords of cells which resembled zona fasciculata and, to a lesser extent, zona reticularis. A few scattered foreign body giant cells with scarring were often present in the fat and fibrous tissue surrounding these modules. Myelinated and non-myelinated nerves and some fairly prominent blood vessels were also commonly noted in the fibrous tissue around these nodules. Some of the small arterioles had fairly prominent and slightly thickened walls with minimal hyalinization.

Summary of Histopathologic Findings. The grafts undergo necrosis followed with regeneration of cells which have the pattern of the zona glomerulosa. A thin band of fibrous tissue demarcates the transplant from the surrounding mesentery. Remnants of degenerated tissue with their granulomatous inflammatory reaction persist for long periods. The regenerating cells are aligned in typical cords bounded by capillaries. These cords of cells progress into the degenerated material of the original graft. The new cords of cells increase in size and ultimately are delimited by thin strands of fibrous tissue with the formation of small nodules resembling those which are commonly noted in nodular adrenal cortical hyperplasia.

BLOOD CORTICOID RESPONSE TO INTRAVENOUS ADRENOCORTICOTROPHIN

The values of blood 17,21-dihydroxy-20-ketosteroids were determined by a modification of

TABLE III

RISE IN BLOOD CORTICOID VALUES AFTER INTRAVENOUS ACTH

	No. of Cases	Fasting Values (μg./100 cc.)	No. Responding	Values after ACTH (μg./100 cc., mean interval 1 hr.)
Controls	11	14.3 (S.D. 9.2)	10	25.4 (S.D. 10.4)
Patients	12	4.1 (S.D. 3.6)	7	13.8 (S.D. 6.2)
Addison's disease*	7	5.1 (S.D. 5.7)	0	None responded
Adrenalectomized-oophorectomized†	3	3.1 (range 2.8–3.5)	0	None responded

* From published data of Christy et al.[19]
† From published data of Sweat.[20]

the method of Silber and Porter.[18] Since this test was available only during the latter part of our investigation, it has not been performed in all of the cases. (Table III.)

Eleven normal women in the menopause, with an average age of fifty-four years (range forty-six to sixty), were injected with intravenous ACTH and served as controls. The test was performed in the morning, in the fasting state, at rest. Thirty milligrams of ACTH (Armour) dissolved in 250 cc. of 5 per cent glucose were administered intravenously as rapidly as possible, usually within ten to twelve minutes. Blood samples were drawn before the administration of ACTH and at various intervals up to three hours. Eosinophils were measured in the fasting state and three hours after the administration of ACTH. One of the control patients did not respond to the ACTH with either a rise in corticoids or a fall in eosinophils, and refused further investigation; therefore she was not included in the tabulation. The other ten control women had an average fall of 70 per cent in the number of circulating eosinophils three hours after the injection of ACTH. In five of the ten patients tested there was a 40 per cent drop in the number of circulating eosinophils; the remaining five showed no fall. We have taken the liberty of including seven documented cases of Addison's disease as reported by Christy et al.,[19] since the method of measurement was approximately the same and the lack of corticoid response was uniform. In addition, three adrenalectomized-oophorectomized patients of Sweat[20] had a fasting corticoid level similar to that of our patients and none responded to ACTH. These added controls strongly suggest that at least half of our patients have functional adrenal cortical tissue.

URINARY 17-KETOSTEROIDS AND CORTICOIDS

It is of interest that in almost all of the patients the urinary 17-ketosteroids and urinary 17,21-dihydroxy-20-ketosteroids were present in small amounts similar to that observed in Addison's disease. In rare instances 17-ketosteroid and/or corticoid excretion as high as 7 to 9 mg.* per twenty-four hours was recorded six months after transplantation. Even in those cases which showed a plasma corticoid rise after ACTH stimulation, an increased urinary steroid output did not occur.

At present the most reliable method for evaluating the physiologic activity of the grafts is by measuring the elevation of the plasma corticoids following the intravenous administration of ACTH.

COMMENTS

Previous attempts at autografting of the adrenal cortex independent of its blood supply have been unsuccessful.[21–23] According to a recent report by Grayhack and Harris,[15] three dogs were implanted with four to five intrasplenic grafts, and one animal was implanted with subcutaneous grafts. They supported their animals with DCA and eschatin® for as long as seventeen days; and when therapy was stopped, all animals died. It may be that the dogs were not maintained long enough for successful functioning of the grafts. In none of these experiments was ACTH administered to stimulate the grafts, and this may be the essential prerequisite for successful autografting of the adrenal cortex. The adrenal cortical substitutes administered may have resulted in an inhibition

* Normal range of 17-ketosteroid 5–15 mg./24 hour; corticoid 3.5–7.5 mg./24 hour.

of endogenous ACTH production by the pituitary. Moreover, in no instance did the aforementioned investigators report on removing the adrenal medulla before grafting so the epinephrine would not cause local vasoconstriction and inhibit vascularization of the grafts. This phenomenon was reported in guinea pigs,[23] and may be a significant factor for successful transplantation of the adrenal gland of both the dog and human.

It is of interest to speculate on the effect of the liver on adrenal secretions when they are released directly into the portal circulation. *In vitro* experiments indicate that perfusion of the rat liver with cortisone and hydrocortisone results in some transformation of these steroids.[24] Paschkis et al.[25] and Louchart and Jailer[26] showed that the glycogenic activity associated with cortisone is distinctly lowered by incubation with rat liver slices. However, *in vivo* experiments in the same animal have shown that the transplanted adrenal with primary hepatic drainage is compatible with life processes;[7–10] and if resistance to hypoglycemia is some measure of glycogenic activity of the adrenal cortex, such animals are more resistant to hypoglycemic convulsions than adrenalectomized animals.[11] The fact that rats can be completely maintained without added support when, after adrenalectomy, the adrenal gland is placed in the portal circulation, may be due to the fact that sufficient cortical tissue regenerates to meet ordinary adrenal steroid body needs, and/or that the rat steroids most essential for life processes are not modified by the liver to a less effective form.

In the human, cortisone and hydrocortisone are effective by oral administration, which may infer physiologic activity of the drug after hepatic passage unless absorption from the intestine is by way of lymphatics, thus bypassing the liver. However, the fact that hydrocortisone disappears from the blood at a slower rate in humans with liver disease indirectly suggests that the liver may play an active role in its metabolism.[27]

In our patients, only three at autopsy showed any sizable quantity of adrenal tissue. That the grafts could not quantitatively produce enough steroids to support life is suggested. However, it is our belief that in certain cases the grafts did make some steroid contribution, as evidenced by: (1) the lesser steroid support required in some of the patients, and (2) the rise in plasma corticoids in seven patients after the intravenous administration of ACTH.

The possibility of accessory adrenal cortical tissue cannot be completely ruled out. Graham[28] reported that approximately one of three routine autopsies showed such tissue. However, in none of our autopsied cases has any accessory adrenal tissue been found.

In this clinical experiment, since many variables are active, it is impossible to attribute objective improvement to the adrenal grafts. Even in those patients who had been previously castrated and had been given courses of steroid therapy with progression of the disease and who then showed improvement after the performance of our procedure, one still queries, "Is it the adrenalectomy or the adrenalectomy with transplantation that induced the favorable result"? In a series of this small size in which five of sixteen patients are still alive, it would be both unscientific and hazardous to make any therapeutic deduction. However, one wonders if the liver has altered the adrenal steroids to produce a cancer-inhibiting product in those patients with objective improvement in whom there is evidence of physiologic function of the grafted adrenal cortex. This question is under study at the present time.

The only positive and unequivocal result from this investigation at this time is the finding that the adrenal cortex can be autografted in the human being. Although the histologic evidence is incontestable, evidence of physiologic functioning is on more tenuous ground. The decreased steroid maintenance requirements of some of the patients, as well as instances of rise in plasma corticoids after intravenous ACTH administration, can only suggest that in certain instances the grafts may be functioning physiologically.

SUMMARY

1. Autotransplantation of the adrenal cortex to the mesentery, combined with oophorectomy and adrenalectomy was performed in eighteen women with metastatic carcinoma of the breast.

2. This new surgical procedure was based on the following considerations: (*a*) Mammary carcinoma is apparently often under hormonal control. (*b*) Successful autografting of the adrenal gland to the portal circulation has been done in the rat. (*c*) The liver inactivates

estrogens and androgens, which are present in the adrenal secretions and may affect mammary carcinoma. (*d*) After passage through the liver, adrenal steroids essential to life seem to retain physiologic activity and some may be altered to a form which inhibits mammary carcinoma.

3. The operative technic, general medical management and, specifically, the preparation of the grafts are described. The necessity for postoperative administration of ACTH is discussed.

4. In each of the nine patients that came to autopsy apparently viable adrenal cortex was found at the site of transplantation. The age of the grafts varied from 45 to 769 days after operation. In the patient autopsied after 45 days, successful grafts were observed in spite of pretreatment of the patient with cortisone for one year and the presence of gross metastases in the donor tissue.

5. In seven of twelve patients a significant rise in plasma corticoids occurred after the intravenous administration of ACTH, which is considered objective evidence of physiologic function of the grafts.

6. With the exception of two postoperative surgical deaths, clinical improvement occurred, even though transient, in all but three cases and is sustained for from sixteen to twenty-eight months in five current cases. It is too early to evaluate the therapeutic role that this procedure may have in the treatment of carcinoma of the breast.

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DISCUSSION

HORACE J. MCCORKLE (San Francisco, Calif.): Dr. Bell gave me a copy of the paper by Drs. Bernstein, Biskind and Brown, and asked me to say a few words about our experiences with grafting of adrenal cortical substance and with adrenalectomy for the palliation of certain selected patients with advanced cancer of the breast.

First, in our laboratory the late Dr. Frederick Kreutzer confirmed the possibility of transplanting adrenal cortical grafts in dogs. He and Dr. Allen Johnson did this successfully before the work was attempted in human patients.

Since 1946 we have studied our patients with advanced cancer of the breast in a clinic established by the late Dr. Low-Beer, Dr. Bell and me, and we have selected certain cases for the investigation of various types of therapy for palliation of advanced cancer of the breast. In connection with this work, patterned after that of Dr. Huggins who visited us in 1953, we did grafts in two cases.

Dr. Galante grafted adrenal tissue into the spleen in one case in which a bilateral adrenalectomy was performed. The spleen was selected because of the fact that in the animal experiments the spleen seemed the best place to receive the graft. The patient lived for a little more than a year and died with advanced cancer of the breast in April, 1954. A specimen was removed at autopsy. The patient had required replacement therapy with adrenal cortical substance throughout the postoperative period. Apparently the graft survived but did not function adequately enough to sustain the patient without medical therapy.

The second case was treated at about the same time and this patient is still living. She also requires full doses of adrenal cortical substance to sustain her.

Because of the fact that these two patients both required full doses of medical therapy, Dr. Galante devised this other procedure. Following right adrenalectomy the adrenal vein was anastomosed to the splenic vein. This was done purely as an investigational procedure and was not applied to routine treatment of patients who have advanced cancer of the breast. In these few selected cases Dr. Galante has had at least one patient able to get along without sustaining cortisone therapy unless she comes to a stress period. If she becomes ill or subjected to some unusual stress, she requires some additional adrenal cortical substance.

These procedures, of course, are not advocated as clinical measures. They were done as part of an investigation in our advanced breast tumor clinic and it is our belief at this time that probably it is not indicated to use any sort of graft in connection with the adrenalectomy-oophorectomy procedures in our patients with advanced cancer of the breast, the reason being largely that it is relatively easy to sustain the patients medically with cortisone. This therapy is so easy and satisfactory that the somewhat more difficult grafting procedures seem hardly worth while.

In the studies of Drs. Bernstein, Biskind and Brown it would appear from examining the case records that their patients have been able to get along for at least a time on smaller than usual doses of medical therapy. This, of course, may be theoretically worth while because when our patients live for a year or two or three and are kept on full doses of cortisone therapy, osteoporosis develops and sometimes the pain of discomfort from the osteoporosis is a real problem. At this time we are giving small doses of testosterone which seem to be helpful in palliating the painful condition resulting from prolonged medical therapy with cortisone.

This is a problem that possibly the authors may help avoid if their grafts function better than ours did.

At this time we select only certain patients for adrenalectomy for advanced cancer of the breast. The chief contraindication is extensive disease in the liver. If the patient is jaundiced from hepatic metastasis or if there is other evidence of hepatic metastases, it seems hardly worth while to put the patient through this surgical procedure.

In patients with metastases to the spine and other bones, and those with abdominal and pleural metastases with a great deal of fluid in the chest or abdomen, palliation has been obtained in some cases for a period of some months up to approximately three years after adrenalectomy-oophorectomy; the well-being of some of these patients on cortisone therapy is certainly something very pleasant to see. The treatment of patients having advanced cancer of the breast with cortisone therapy alone requires much larger doses than we use after adrenalectomy-oophorectomy. These patients get into difficulties with cortisone therapy much sooner than do those who have had adrenalectomy or oophorectomy. Adrenalectomy-oophorectomy has been used as an excellent palliative procedure in certain selected patients with advanced cancer of the breast in our advanced breast tumor clinic.

You might be interested to know how we make our selection of patients for this procedure. We have several things which are helpful to patients with advanced cancer of the breast. The first of these is x-ray therapy. Patients beyond surgical treatment can often have successful palliation with x-ray therapy for long periods of time. As long as they can be kept comfortable with this measure, we do not consider any type of hormone therapy. When control with x-ray therapy fails, we then usually use either estrogen or androgen therapy, and in patients with bone metastases our best results have been with androgen therapy. Premenopausal patients, regardless of the type of metastases, are receiving palliation with the use of androgen. With patients several years beyond the menopause, particularly those who have soft tissue and pulmonary lesions, palliation sometimes can be obtained with large doses of estrogens. When control with these measures fails, we have used nitrogen mustard or nitrogen mustard in connection with hormone therapy. Whether this actually helped palliate patients with cancer of the breast we cannot be sure, but there have been two cases in which it seems that the use of nitrogen mustard has been helpful. When all other palliative methods have failed, adrenalectomy-oophorectomy may be indicated.

Our best results in palliating patients with advanced cancer of the breast have been with the adrenalectomy-oophorectomy procedure. These patients were sustained with medical (cortisone) therapy satisfactorily, so much so that we hesitate to use an adrenal grafting procedure.

GERSON R. BISKIND (closing): I want to thank the discusser for enlarging on this subject and letting us know what others who have investigated it have found.

The subject of the relationship of cancer of the breast to hormones is a very complicated field to try to summarize briefly, but as indicated by others there seems to be no doubt that there is some very definite relationship. If we are ever able to ascertain which of the cancers of the breast are truly hormone-dependent, I think we will have made a major step forward, because then it may be possible to select the proper type of treatment for a specific tumor.

That there are hormone-dependent tumors was first shown in our animal experiments reported in 1944. The castration of the female rat with transplantation of one ovary to the spleen produces an alteration in the hormone balance. The estrogenic hormones elaborated by the ovary must now pass directly to the liver where they are inactivated and can no longer affect the hypophysis. The latter undergoes a castrate change and its gonadotrophic hormones stimulate constantly the transplanted ovary. This ovary grows in size due to formation and enlargement of the corpora lutea which no longer involute. After approximately five months a luteoma appears, and after another five months this tumor grows into a granulosa cell tumor. This change from normal tissue to neoplastic tissue was the first demonstration that an alteration of the hormonal balance *in vivo* could produce a neoplasm.

Using these experiments as a pattern, other tissues were transplanted to the portal circulation to obtain hepatic inactivation of the substances they elaborated. It was shown that in the adrenalectomized rat the transplanted adrenal cortex would grow in the mesentery and was capable of supporting life and certain other functions. The transplantation of an ovary and an adrenal into the portal circulation of a castrated, adrenalectomized rat produced an inhibition of the growth of the ovarian tumor. This led us to infer that the liver may alter some of the adrenal secretions into a tumor-inhibiting substance. On the basis of these experiments in rats, the human experiments were tried.

I think that the animal and human experiments we have described offer possibilities for a considerable amount of fruitful investigation into the relationship of the hormonal balance in the production and growth of certain tumors.

The Effect of Alterations of the Mucosa of the Gastroesophageal Junction upon Gastric Reflux into the Esophagus

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From the Surgical Research Laboratories of the Stanford University School of Medicine, San Francisco, California. Aided by Grant A-239, United States Public Health Service.

REGURGITATION of the gastric contents into the esophagus is advanced commonly as the cause for the development of peptic esophagitis in man. Although the exact mechanism whereby regurgitation of gastric contents into the esophagus is prevented is not known, it is known that esophagitis frequently is seen in association with esophageal hiatus hernia. It is presumed that this association occurs because the development of the hernia destroys the method of sphincteric control of regurgitation.

Unfortunately, it also is common knowledge that asymptomatic esophageal hiatus hernias are common incidental findings, especially in the older age group of patients.

An explanation for these two opposing facts can be found in the suggestion that it is the angle of entrance of the esophagus into the stomach which under normal conditions forms a flap valve so that regurgitation will not take place. It has been shown (see following paper) that if this angle is maintained, then even if a hernia is present, regurgitation will not take place. These are the patients in whom esophagitis does not develop. If the hernia allows this angle to be obliterated, symptoms then appear as the regurgitation takes place constantly, thus damaging the mucosa of the esophagus.

It is the purpose of this article to show that ... the dog alterations in the mucous membrane in this area do not produce esophagitis as long as the angle of entrance of the esophagus into the stomach is preserved.

METHOD

Young adult mongrel dogs were anesthetized with intravenous anesthesia and an intratracheal positive pressure apparatus put in place. The left chest was opened through the bed of the eighth rib. The mediastinum was opened. A linear incision about 4 to 5 cm. in length was made through the muscularis of the esophagus. The muscularis is a definite, well developed layer in the dog. The mucosa can be dissected free with ease.

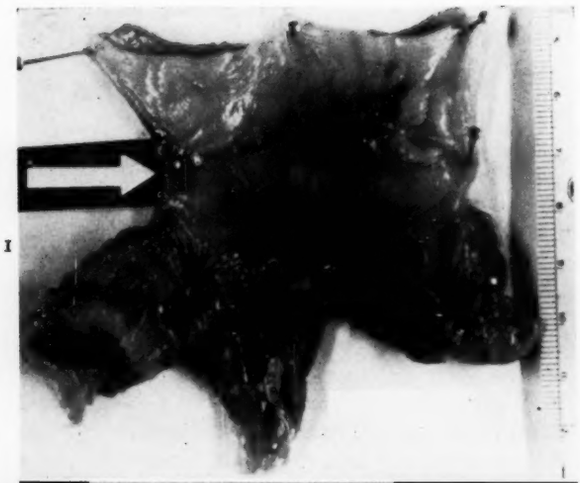
In one group of animals a cylinder of esophageal mucosa 3 to 4 cm. in length was removed. The gastric mucosa then was freed up submucously and sutured to the esophageal mucosa so that gastric mucous membrane extended within the muscular tube of the esophagus to 5 cm. above the diaphragm.

In the second group of animals a full-thickness section of skin was used to replace the defect.

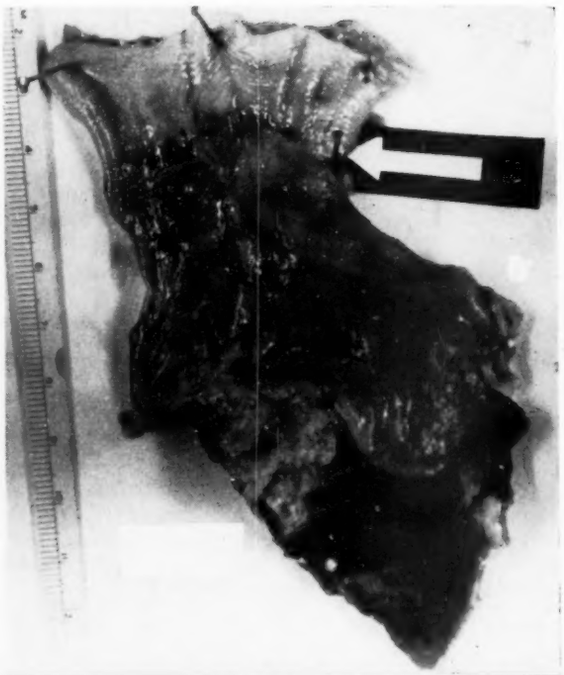
After the graft had been put into place, the muscular coat was closed. The mediastinum and the chest wall were closed without drainage.

The animals were started on liquid feedings on the third day. Esophagoscopy was done after the first six weeks. There were no operative deaths. In one animal a mild stricture developed at the operative site and in another animal an ulcer developed which microscopically appeared to be due to separation of the suture line between the gastric mucosa and the esophageal mucosa. In the other eighteen animals primary healing took place. (Figs. 1 to 11.)

It is apparent that in the dog under normal conditions the presence of the gastric mucous membrane above the normal gastroesophageal



FIGS. 1 to 3. Photographs of the new gastroesophageal junction showing primary healing. All specimens more than eight months after the initial operation.



FIGS. 4 and 5. Photographs of the new gastroesophageal junction showing primary healing. Specimens more than eight months after the initial operation.

junction will not produce peptic esophagitis. It is apparent, further, that skin when placed in the esophagus will either take as a graft or serve as a bridge so that the esophageal mucosa can grow over it.

In a third group of six animals esophagitis was produced by cauterizing the esophagus through the esophagoscope with 10 per cent hydrochloric acid. One week later the esophagus was opened and the inflamed area (Fig. 12) was excised. The defect was covered by gastric mucosa in three cases and by skin in three cases. All of the first group healed without difficulty. In one of the latter group the skin patch sloughed and an ulcer developed. (Fig. 13.)

COMMENTS

The esophagus of the dog and that of man are not strictly comparable. The dog has an

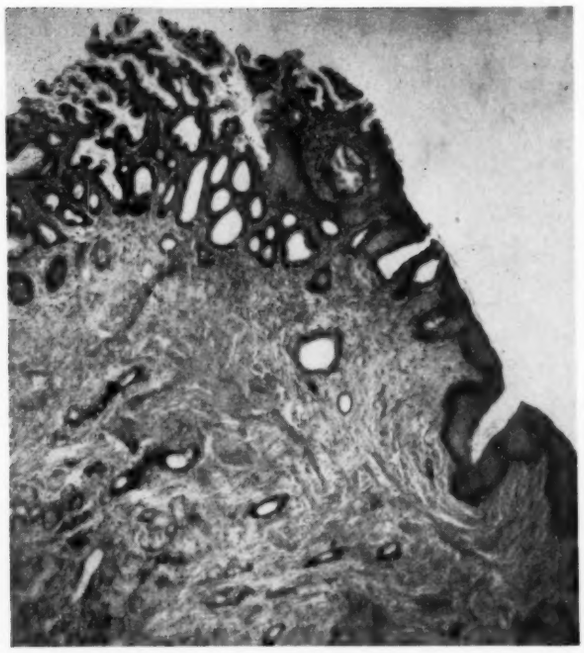


FIG. 6. Photomicrograph showing the junction of the gastric mucosa with the esophageal mucosa at its new level. Note absence of inflammatory cells.

FIG. 8. Full-thickness skin graft in esophagus. Normal healing, but moderate stricture formation by the skin graft, which in this instance was a complete tube.

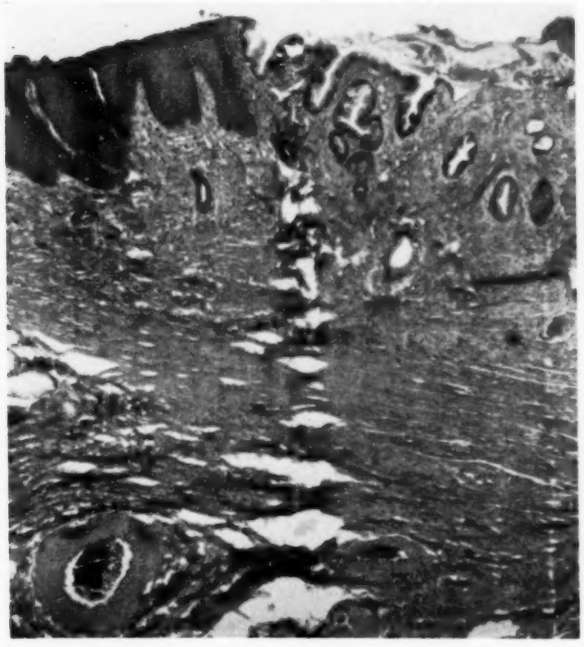


FIG. 7. Photomicrograph showing the junction of the gastric mucosa with the esophageal mucosa at its new level. Note absence of inflammatory cells.

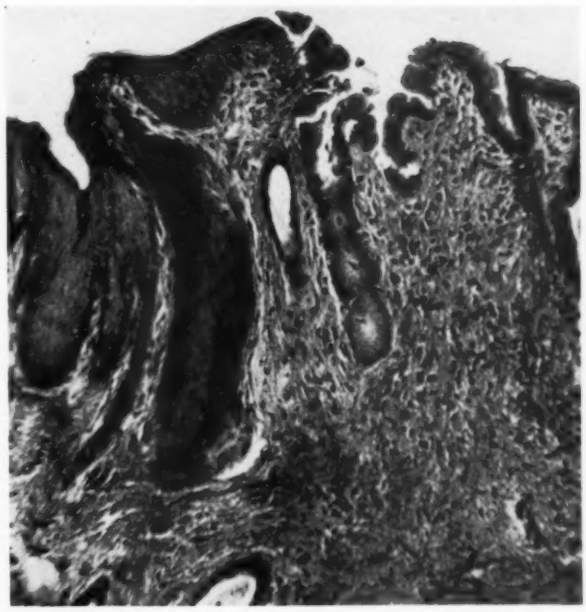


FIG. 9. Photomicrograph of the transplanted skin into the esophagus. The skin elements have all disappeared. In some areas the last remnants of cornification can be seen.

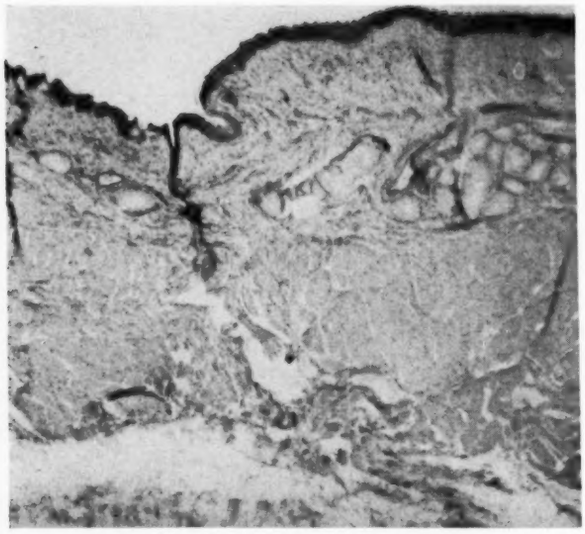


FIG. 10. Photomicrograph of the transplanted skin into the esophagus. The skin elements have all disappeared. In some areas the last remnants of cornification can be seen.

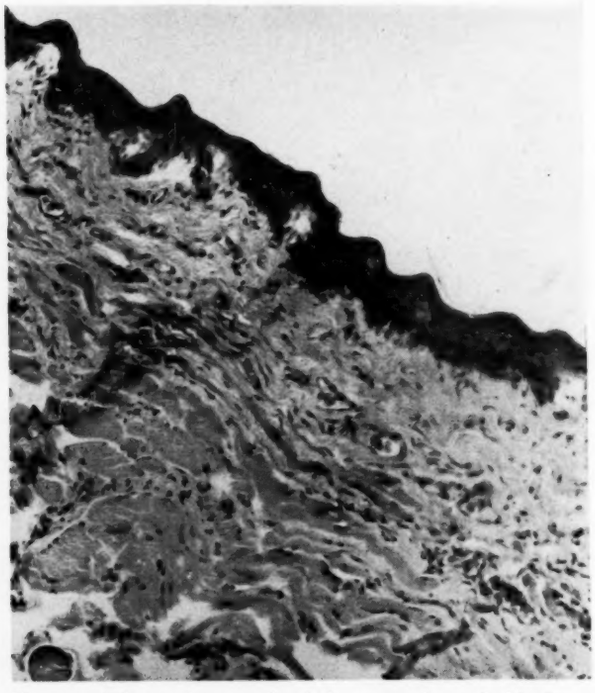


FIG. 11. Photomicrograph of the transplanted skin into the esophagus. The skin elements have all disappeared. In some areas the last remnants of cornification can be seen.

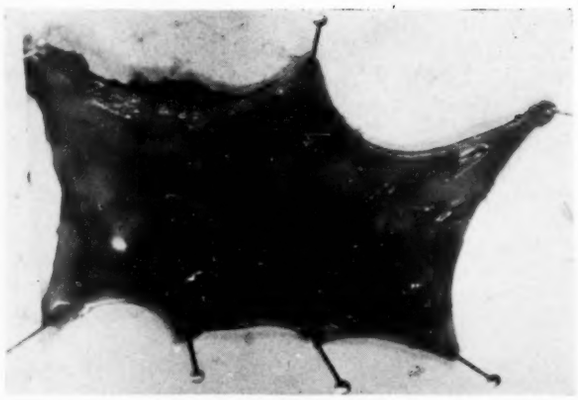


FIG. 12. The size of the inflamed area removed at operation.

FIG. 13. Taken from the only dog in which ulceration developed at the gastroesophageal junction.

excellent muscular coat in his esophagus which is easily kept as a strong layer for suturing purposes. The esophagus of man cannot be handled so easily. Furthermore, the horizontal position of the upper gastrointestinal tract in the dog probably makes for greater ease of reflux in the dog than does the upright position in man. It has been shown repeatedly that damage to the sphincter mechanism in the dog will result in esophagitis.

Merendino,[1] who has studied this problem extensively, has devised a procedure for the interposition of a jejunal segment between the esophagus and stomach, and claims that this segment acts as a sphincter to prevent reflux esophagitis. It is interesting to note that his diagram of the operation shows the jejunum entering the stomach so that an angle similar to the normal esophagogastric angle is reconstructed. The experiments herein reported would suggest that as long as this angle is

preserved, reflux esophagitis will not occur in the large majority of cases in spite of alterations in the character of the gastric mucous membrane junction with the esophageal mucous membrane.

These experiments agree with those of Hoag, Kiriluk and Merendino[2] concerning the importance of the gastroesophageal junction, but would suggest that it is not the mucous membrane which is the important factor.

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Clinical Observations on the Function of the Gastroesophageal Junction

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AN attempt to discover from the literature what anatomic and physiologic mechanism or mechanisms exist for the prevention of regurgitation of gastric contents into the esophagus is most frustrating. Since Helvetius first described a morphologic sphincter in 1719, there has been a continued difference of opinion not only as to whether a sphincter mechanism exists but also, if there is such a mechanism, what the site is at where it exerts its effect. Such careful observers as Lendrum[1] and Lerche,[2] each of whom has dissected more than 100 esophagi, typify the difference of opinion offered in evidence in this problem. Lendrum denies that a sphincter exists, while Lerche is convinced of the accuracy of Helvetius' original description of an anatomic sphincter.

Other mechanisms of control besides an anatomic sphincter have been suggested. The stopcock effect of the diaphragm has been described by Jackson.[3] Dick and Hurst,[5] Negus[6] and Marchand[8] all have offered evidence to suggest that the angle of entrance of the esophagus into the stomach is an important factor in the prevention of regurgitation into the esophagus. It is claimed that under normal conditions the left lip of the gastroesophageal junction acts as a flap valve and is closed tightly the more distended the higher lying fundus becomes. Absence of the ballooning fundus permits regurgitation.

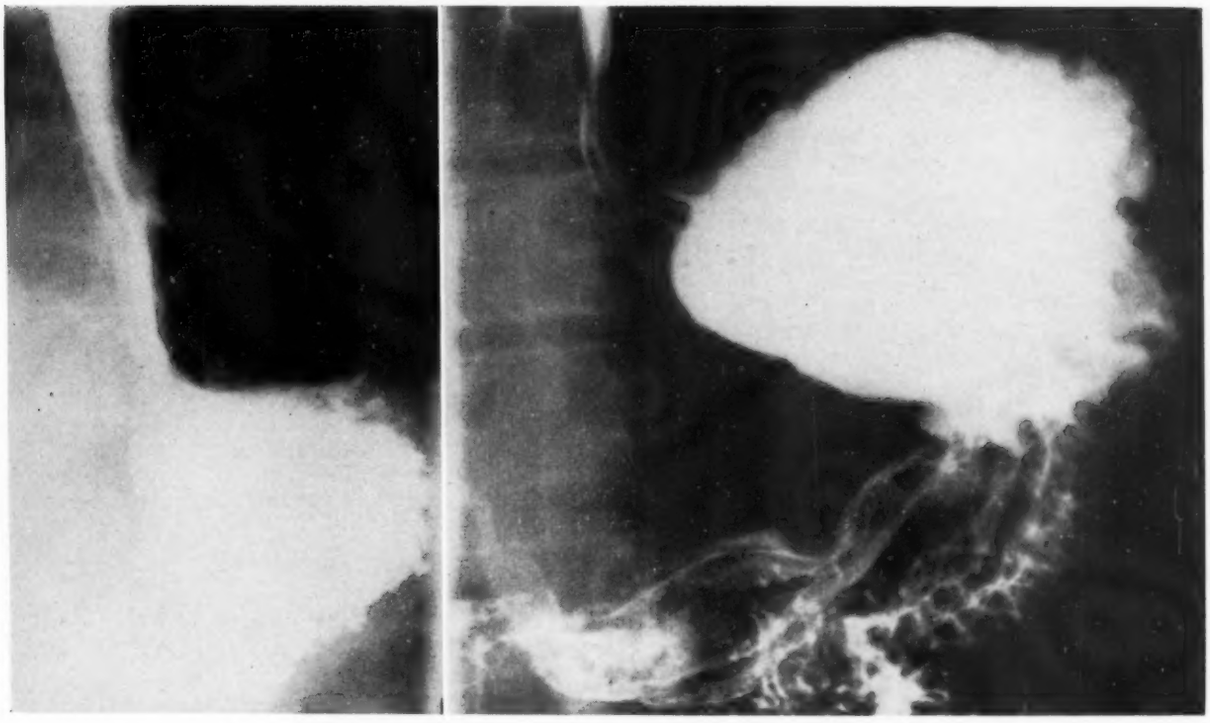
Marchand[8] noted in cadavers that when water was pumped into the pyloric end of the stomach *in situ* in young adults, a pressure of 28 cm. of water was required to cause regurgitation into the esophagus. If the fundus were clamped off so that the stomach had the appearance of that seen in the "short esophagus," only 9 cm. of water pressure were required to cause regurgitation. If the diaphragm were removed so that the fundus could balloon into the thorax, thus increasing the gastroesophageal angle, it required 42 cm. of water pressure to cause regurgitation. Marchand interpreted these data to mean that the angle of the junction of the esophagus with the stomach was of importance in preventing reflux of gastric contents.

It is the purpose of this paper to offer additional evidence in the support of the thesis that the angle of entrance of the esophagus into the stomach is one of the important factors in the prevention of regurgitation of the gastric contents and that Marchand's observations in cadavers can be confirmed in the living patient.

EXPERIMENT I

Ten patients with pulmonary tuberculosis who were being treated with pneumoperitoneum were the subject of the first experiment. None of these patients had digestive symptoms other than a feeling of fullness on the first two days after the pneumoperitoneum refill. It is well known that pressure on the abdominal wall is approximately equal to the intra-abdominal pressure and that the intra-abdominal pressure is approximately equal to the intragastric pressure. Pressure was applied to the abdomen by pumping up a rubber anesthesia bag under a tight abdominal binder. A Y-tube connected to a Tycos manometer gave readings of the approximate pressures.

At fluoroscopy each patient was given 200 cc. of thin barium water. There was no delay in the passage of barium. It was noted in all cases that the angle of the fundus with the



1A 1B

FIG. 1. A, patient T. M., a twenty-six year old man (SFH 140805). Obliteration of gastric angle with pneumoperitoneum; patient in upright position. Regurgitation takes place on overcoming force of gravity. B, patient in supine position. No regurgitation at same pressure.

esophagus was obliterated when the patient was in the upright position (Figure 1A), but that in the prone position the acuteness of the angle was reconstructed. The abdominal pressure then was increased to 40 mm. of mercury. It was noted that there was a marked delay in the passage of the barium in eight of ten cases; and in all cases when the esophageal wave met the stomach, regurgitation of the stomach contents easily could be seen. This type of regurgitation is obviously a pressure phenomenon and ceases as soon as the pressure in the stomach and esophagus are equalized. In contradistinction, the regurgitation of the patient with the hiatus hernia is easily produced and is present constantly when the patient is in the prone position. Regurgitation without swallowing was noted in four instances, all in patients over fifty years of age.

The pressure was released and the patient placed in the Trendelenburg position. It was noted immediately that the stomach floated up against the diaphragm, thus recreating the normal angle of the entrance of the esophagus. (Figure 1B.) When the abdominal pressure was increased to 40 to 50 mm. of mercury, no regurgitation took place in any of the ten patients.

EXPERIMENT II

The identical experiment was repeated on twenty-one patients with small esophageal hiatus hernias.

Figure 2A shows a small hernia in a man sixty years of age who had no digestive symptoms. When abdominal pressure was applied with the patient in the upright position, a fluid level could be seen in the thoracic portion of the stomach (Figure 2B); but in spite of the pressure, no regurgitation took place because the narrow opening through the diaphragm caused an angulation at this point just as in a normal esophageal junction. However, when the patient is placed in the prone position (Figure 2C), contrary to the patients without hernias, the gastroesophageal angle is obliterated so a tremendous amount of regurgitation takes place when the pressure is applied.

Figure 3A shows a hiatus hernia in a man seventy years of age who had a common duct

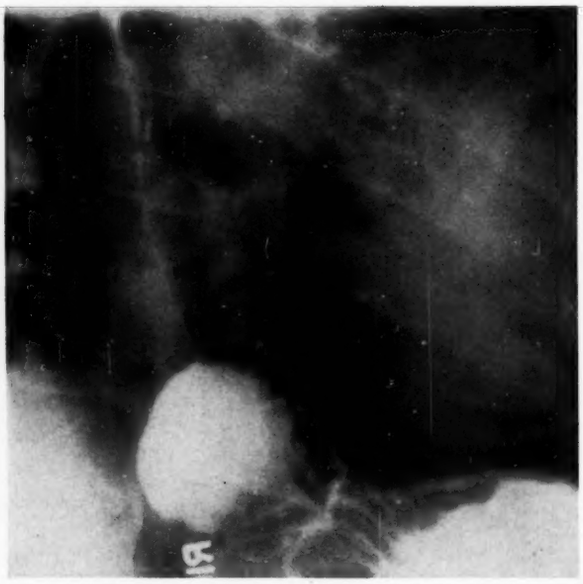


FIG. 2A. Patient J. D., a sixty year old man (SFH 11842). Small hiatus hernia; patient in supine position.

FIG. 2B. Patient J. D. in upright position. Note angle between hernia and remainder of stomach. Abdominal pressure; no regurgitation.

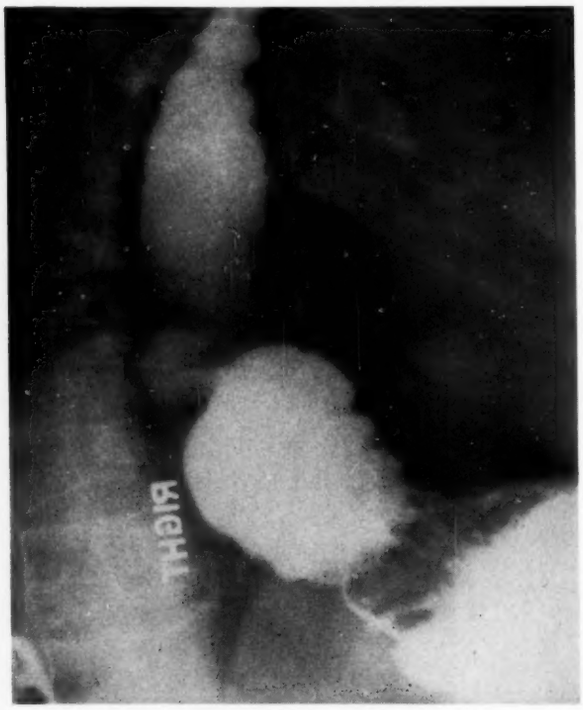


FIG. 2C. Patient J. D. in prone position with abdominal pressure. Note extensive regurgitation.

stone with jaundice. His gastrointestinal symptoms were minimal. With pneumoperitoneum, the hernial sac is filled (Figure 3B) but the contents are not reduced. When 20 mm. of mercury pressure are applied to the abdomen, the hernial sac dilates even more but the stomach does not return to the abdomen. No regurgitation can be demonstrated.

Figure 4A shows a small hiatus hernia in a woman fifty-three years of age with cirrhosis of the liver and hermatemesis. Pressure of only 25 mm. of mercury caused mild regurgitation when the patient was in the upright position and extensive regurgitation when the patient was in the prone position. (Figure 4B.)

Figure 5A shows a large hiatus hernia in a woman sixty-eight years of age who had had vague gastric symptoms for many years. The present hospital entry was for treatment of a perforated diverticulum of the sigmoid. With the patient in the upright position with increased intra-abdominal pressure to 40 mm. of mercury there was regurgitation into the thoracic stomach (Fig. 5B) but none into the esophagus. With the patient in the prone position with no pressure (Fig. 5C) the hernia filled out but still no esophageal regurgitation was noted. When pressure was applied with the patient in the prone position, slight esophageal regurgitation occurred. (Fig. 5D.)

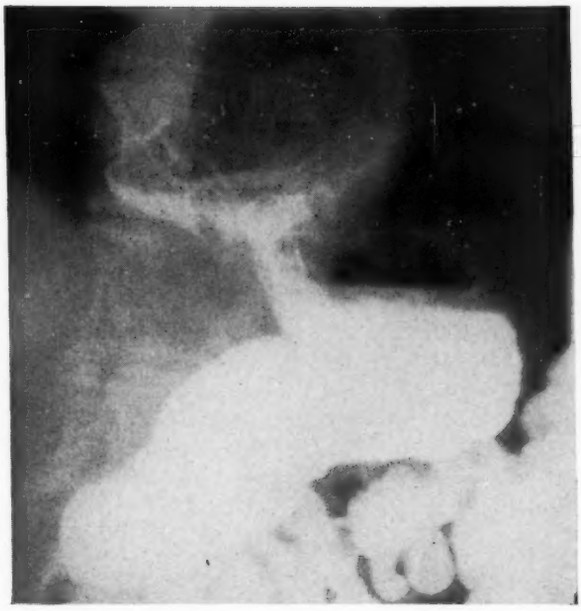


FIG. 3A. Patient G. L., a seventy year old man (SFH 143996). Asymptomatic hiatus hernia; patient in upright position.

FIG. 3B. Patient G. L. in prone position with pneumoperitoneum and abdominal pressure. No regurgitation takes place.

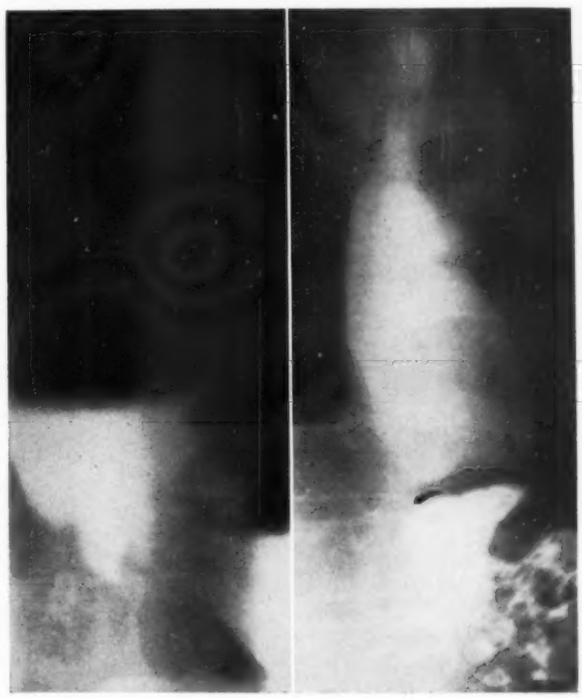
TABLE 1

SUMMARY OF TWENTY-FOUR CASES OF HIATUS HERNIA

Associated diseases (22 patients):	
Cirrhosis	4
Tuberculosis	1
Diverticulitis	1
Fracture	4
Jaundice	1
Arteriosclerosis	5
Arthritis	2
Peripheral circulatory disease	4
No demonstrable regurgitation	10
Associated gastrointestinal symptoms (15 patients):	
Mild (regurgitation present)	8
Mild (no regurgitation)	5
Severe (marked regurgitation)	2

COMMENTS

It is difficult to ascertain how frequently esophageal regurgitation is seen on routine gastrointestinal examination. According to Sweet,[7] his radiologic department claims to demonstrate gastric reflux in nearly every case. We have not found this to be true in the normal young adult. Regurgitation occurred only under the artificial conditions where pneumoperitoneum changed the anatomic arrangement of the esophagus to the cardia of the stomach and extremes of pressure were applied to the abdomen. In those instances of the normal patient where slight regurgitation took



4A 4B

FIG. 4. A, Patient M. LeB., a fifty-three year old woman with cirrhosis of the liver and hematemesis. Patient in upright position with delay at junction in absence of pressure. B, pressure applied; marked regurgitation.

FIG. 5A. Patient J. T., a sixty-eight year old woman. Patient in upright position. No delay without pressure.

FIG. 5B. Patient J. T. in upright position, with 40 mm. of mercury pressure. Regurgitation takes place into thoracic stomach but not into esophagus.

FIG. 5C. Patient J. T. in prone position. No delay in esophageal emptying.

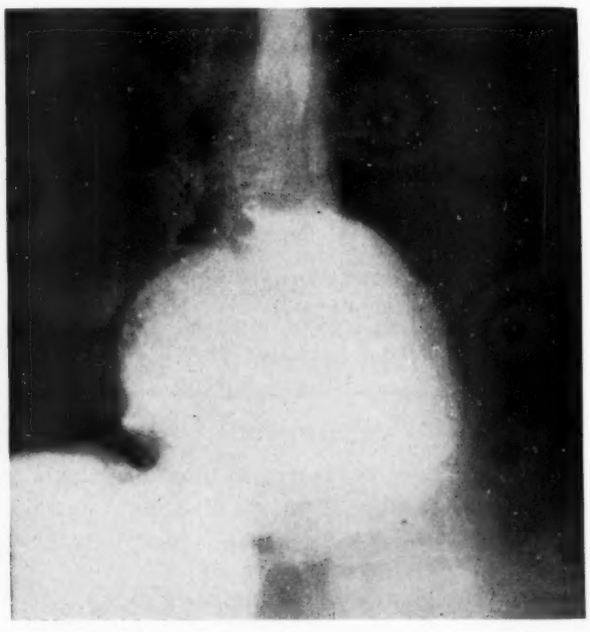


FIG. 5D. Patient J. T. in prone position with 40 mm. of mercury pressure. Moderate regurgitation into esophagus.

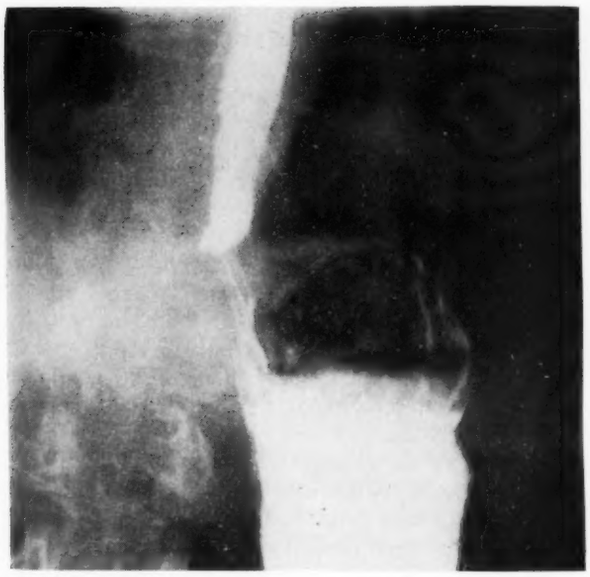


FIG. 6A. Patient E. G., a seventy-two year old woman. Patient in upright position, with pressure. Delay but no regurgitation.

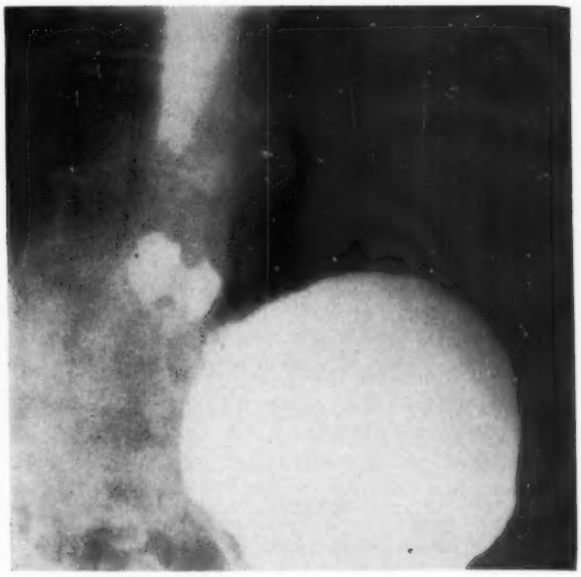


FIG. 6B. Patient E. G. in prone position with pressure. Note phrenic ampulla.

place, all of the patients belonged to the older age group.

When a hiatus hernia is present, the angle may or may not be obliterated. Unfortunately, it is true that it is not so easy to be certain that a small hiatus hernia exists. Allison[9] has pointed out that the level of the junction of the gastric and esophageal mucous membranes is not a fixed point so that it is quite possible that gastric mucous membrane can be found in the esophagus even though the gastroesophageal angle is still present. Radiologically, this picture can be equally deceptive. Figure 6A shows no evidence of hernia in a woman seventy-two years of age in whom abdominal pressure had been applied while she was in the upright position. The barium water is delayed in the esophagus. Figure 6B, with the same patient in the prone position with pressure, shows what might be considered a hiatus hernia but which probably is only what Marchand calls the "phrenic ampulla" and not a true hernia at all. This type of x-ray picture might account for the failure to find a hernia described by the radiologist at the time of operation.

In this small series of hiatus hernias we have been unable to demonstrate regurgitation into the esophagus in every case. Furthermore, not every patient in whom regurgitation was demonstrated complained of symptoms that could be ascribed to the hernia. However, in the only two cases in which bleeding was part of the picture, marked regurgitation was noted in association with the hernia and in both instances peptic esophagitis was present at esophagoscopy. In both of these cases no esophagogastric angle was present, the esophagus entering the stomach at its highest point.

The evidence presented would suggest that the angle of the junction of the esophagus with the stomach does play an important part in the prevention of regurgitation of gastric contents into the esophagus, although it is obviously not the only factor involved. It is possible that by utilizing this principle in operations involving the gastroesophageal junction, postoperative esophagitis and stricture may be prevented.

SUMMARY

Evidence is presented which emphasizes the role of the gastroesophageal junction in the control of regurgitation of gastric contents into the esophagus.

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DISCUSSION

Carleton Mathewson, Jr. (San Francisco, Calif.): I have followed the studies of Drs. Close, Magladry and Cohn with more than usual interest because they are concerned with a fascinating problem which has confused me for many years. It seems incredible in light of the exhaustive studies that have been reported that there still could be a difference of opinion concerning the nature of the sphincter mechanism at the cardia. Dr. Cohn's experimental studies would seem to throw some light on the subject but still leave many well known phenomena unexplained.

The work reported here seems to support the opinion of other observers who have stressed the importance of the esophagogastric angle in relation to the sphincter mechanism of the cardia. These studies also substantiate those of Marchand, who has shown that regurgitation phenomena primarily are due to pressure differences between the esophagus and the stomach, and that regurgitation from the stomach into the esophagus would be continuous if there were not some arrangement to resist the force of intraperitoneal pressure.

Clinically, one recognizes a number of causes of symptomatic gastroesophageal regurgitation. Reflux dyspepsia related to dietary indiscretions, adiposity, cholecystitis, duodenal ulcer, air swallowing, heart disease, pregnancy and hiatus hernia are well known. Although the amount of regurgitation that accompanies each of these conditions may vary a good deal, the symptoms are similar because the effect of each is to cause regurgitation. Correction of the underlying cause in each of these situations, whether it be by simple change in diet, weight reduction or surgery, will relieve the regurgitation without alteration in the cardioesophageal angle. Other factors must therefore have been involved.

The same type of controversy has arisen in connection with delayed emptying of the esophagus, a disorder which results in dilatation and elongation of the gullet. The theories of spasm (cardiospasm) and failure of relaxation (achalasia) have been expounded and are still unsettled. Although an anatomic sphincter within the wall of the esophagus has not been proved, section of the longitudinal and circular musculature does correct the delayed emptying, although at the same time it is apt to result in regurgitation even though the cardioesophageal angle has not been disturbed. Where does this leave us? I think we can safely say that a sphincter mechanism does exist. Whether this is intrinsic within the esophageal wall due to the esophagogastric angle, extrinsic to the esophagus in the diaphragm or a combination of the three cannot be stated positively. Whatever the mechanism, it is an extremely sensitive one which is affected by relatively minor changes in intragastric tension. Prolonged and persistent regurgitation leads to esophagitis which in turn may lead to ulceration, fibrosis and stenosis, whereas the regurgitation that occurs regularly during and after meals or inconstantly in association with disease does not lead to anatomic changes in the esophagus.

Hiatus hernia, as we all know, is frequently asymptomatic; however, the sliding type of hernia may be accompanied with severe and persistent regurgitation. Following disruption of the esophagogastric angle, reflux is produced whenever gastric pressure is increased; this reflux occurs almost constantly, resulting in continuous trauma. The esophagus undergoes inflammatory changes and the symptoms of regurgitation dyspepsia are aggravated by the development of esophagitis. This usually can be corrected by reduction of the hernia so that the stomach remains below the crura of the diagram and the normal esophagogastric angle is re-established. This can be accomplished simply when the esophagus is of normal length; however, when shortening has occurred, it is not possible to restore the esophagogastric angle and most attempts at surgical repair are doomed to failure. It is this situation that has led Merendino to resect the lower end of the esophagus and replace it with a section of jejunum, which he believes acts as a physiologic sphincter. It seems to me that our attention has been focused so strongly on the cardiac sphincter mechanism and that our efforts here, as elsewhere in the body, to produce an artificial sphincter have been so wrought with failure that our attention has been diverted from the more logical solution to the problem, i.e., to establish some sort of a balance between the cardiac and the pyloric sphincter mechanisms so as to prevent gastric tension and the resultant regurgitation.

I have been impressed, as have been Sweet, Burford and others, with the observation that frequently reflux esophagitis is permanently relieved by procedures that correct gastric retention. Pyloroplasty, pylorectomy or gastroenterostomy

alone may overcome regurgitation into the esophagus by the simple means of eliminating the resistance of the pyloric sphincter to gastric emptying. If the stomach can empty more easily into the small intestine below than into the esophagus above, the pressure gradients necessary to cause reflux esophagitis can be prevented. These simple procedures may fail in the advanced cases of acquired or congenitally short esophagus but should be given a trial before more radical operations are undertaken.

RALPH H. LOE (Seattle, Wash.): I enjoyed Dr. Cohn's remarks on the sphincter mechanism of the lower end of the esophagus and his emphasis on the angle of entrance into the stomach. I have been interested in gastroscopy for twenty years and esophagoscopy for a shorter time, and am thus quite cognizant of the angle about which he speaks. On entering the stomach one always is conscious of the swing to the left which the terminal esophagus makes. This is absent in a sliding hernia.

There are other valve mechanisms besides the angle of entrance which are important. Despite the fact that the cardiac muscle sphincter is weak, I think it is still of some importance. There are five or six mechanisms of importance.

The pinchcock mechanism of the diaphragm is probably of little value. However Chevalier Jackson years ago thought it of great importance.

The interdigitation of the folds of the gastric mucosa guard the entrance of the esophagus into the stomach. If one does esophagoscopy on the operating table through the stomach, it is difficult to pass an esophagoscope up into the lower end of the esophagus unless he pulls down and straightens out the angle of the esophagus. At the same time, the folds of the mucosa are partially straightened so that one may see the tightened sphincteric orifice of the esophagus.

The air bubble of the fornix probably helps keep constant pressure on the left side of the angle of the esophagus. The elastic esophagophrenic ligaments spoken of by Allison tend to return the esophagus to normal relationship with the diaphragm and the stomach after swallowing or vomiting. In addition, other factors tend to preserve normal relationship such as tissue attachments, the left gastric artery, peritoneum and the vagus nerve. We are all familiar with the marked loosening effect of vagotomy on the lower end of the esophagus when one wishes to perform total gastric resection from the abdomen.

Fortunately many factors are involved in the esophageal valve mechanism. The elimination of one does not mean that reflux will result. For instance, in the Heller operation sphincterotomy seldom results in regurgitation in contrast to esophagogastrostomy. Shortly before I left Seattle I asked Dr. Harkins, who has been performing a great many Billroth I operations, what his incidence of postoperative esophageal regurgitation was. One might suspect that it would be high, since in this operation one straightens out the angle. In about 450 cases Dr. Harkins was aware of two patients with mild regurgitation. In my own practice, if possible, when operating for cancer of the stomach I have saved approximately 1 inch of the upper end of the stomach, completing the anastomosis either as a Billroth I or II procedure. Postoperative x-rays with the patient in the Trendelenburg position plus pressure have not shown regurgitation. In these procedures much of the angle of entrance is eliminated. Therefore, although I agree with Dr. Cohn that the angle of esophageal entrance is important, I cannot agree that it is all important.

ROY COHN (closing): Having four small children, I am cognizant of the regurgitant effect in the esophagus in infants; so when we have a chance to give barium to a small child, it is interesting to note that the angle is not present, which may account for the ease with which children can actually regurgitate.*

I am not quite so sure in the Heller operation that the angle is not obliterated. Our personal experience with the Heller procedure is not great, but from the experience of others there seems to be a great deal of esophagitis occurring late after this operation. I do not know exactly how various surgeons perform this procedure but in the operations I have seen the angle is actually obliterated.

The same thing is true with the question of the angle in connection with the Billroth I procedure. We have had an opportunity to study only one patient having a Billroth I operation with this point in mind, and that was some eight months after surgery. Much to the astonishment of those of us interested in this problem, the angle seemed to have been reconstituted. One would naturally think, as Dr. Loe said, that by dragging the greater curvature down to make the anastomosis you would probably eliminate it. As we all know, the dilatory powers of the stomach are very great.

* Dr. Cohn illustrated this portion of his discussion with slides of two infants, showing the esophagus apparently coming off the apex of the fundus; no angle was noted at the junction.

Vagotomy and Pyloroplasty in the Treatment of Duodenal Ulcer

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DURING the past six years the operation of vagotomy and pyloroplasty has been the preferred method of surgical treatment of duodenal ulcer at the Veterans Administration Hospital in Long Beach, California. More than 500 operations have been performed during this period. This report deals with the selection of patients for the operation, the technic used, and the pre- and postoperative management. Two hundred consecutive cases with follow-up studies of two years or more have been selected from the total group for an analysis of the results.

The Dragstedt operation of vagotomy is based on the theory that gastric acidity is abnormally increased by neurogenic stimuli which result from certain types of mental stress, and that it is this increase in acidity which is responsible for chronic duodenal ulceration. Sectioning of the vagus nerves prevents the abnormal stimuli from reaching the stomach, with the result that the acidity is reduced to levels below the threshold of ulceration. Dragstedt has produced convincing clinical evidence that vagotomy is an effective means of controlling the disease, and his results have been confirmed by others.[1–5]

Because vagotomy is frequently followed by prolonged gastric retention, it is necessary to add some type of procedure to facilitate emptying. Gastrojejunostomy, one of the methods commonly used, has several disadvantages. It disturbs the normal continuity of the digestive tract and thus interferes with the normal process of digestion. It invites the possibility of ulceration at the site of anastomosis. Diffuse inflammation of the gastric mucosa may result from regurgitation of jejunal contents.[6] Recently Harkins and associates[7] have called attention to the hypersecretion of acid which results from stimulation of the antrum by the circus movement which is established when the jejunum is anastamosed to the stomach. It is possible that in some cases at least this overstimulation nullifies the effect of vagotomy.

Theoretically, a simple pyloroplasty would appear to be the best means of facilitating emptying after vagotomy. It does not alter the normal continuity of the gastrointestinal tract. The possibility of jejunal ulceration is eliminated. The pyloroduodenal mucosa may be inspected during the operation, an important consideration when the diagnosis is in doubt. It is simple to perform; consequently it carries with it a low surgical morbidity and mortality rate. If a second gastric operation should be necessary, it can be performed more easily after pyloroplasty than after gastrojejunostomy or gastrectomy.

The difficulty with pyloroplasty as it is usually performed is that it often fails to provide adequate emptying. This is due to the fact that the multiple rows of sutures ordinarily used in closing the pyloroplasty incision cause an infolding of tissues which constricts the lumen and thus jeopardizes the patency of the canal. This excessive infolding is avoided by the simple expedient of using only one row of sutures in making the closure. We have now used the Heineke-Mikulicz principle with one-layer closure in more than 500 patients without a single occurrence of leakage, and with an acceptably low incidence of postoperative retention.

OPERATIVE TECHNIC

Much of the success of the operation depends upon correct technic. It is our opinion, based

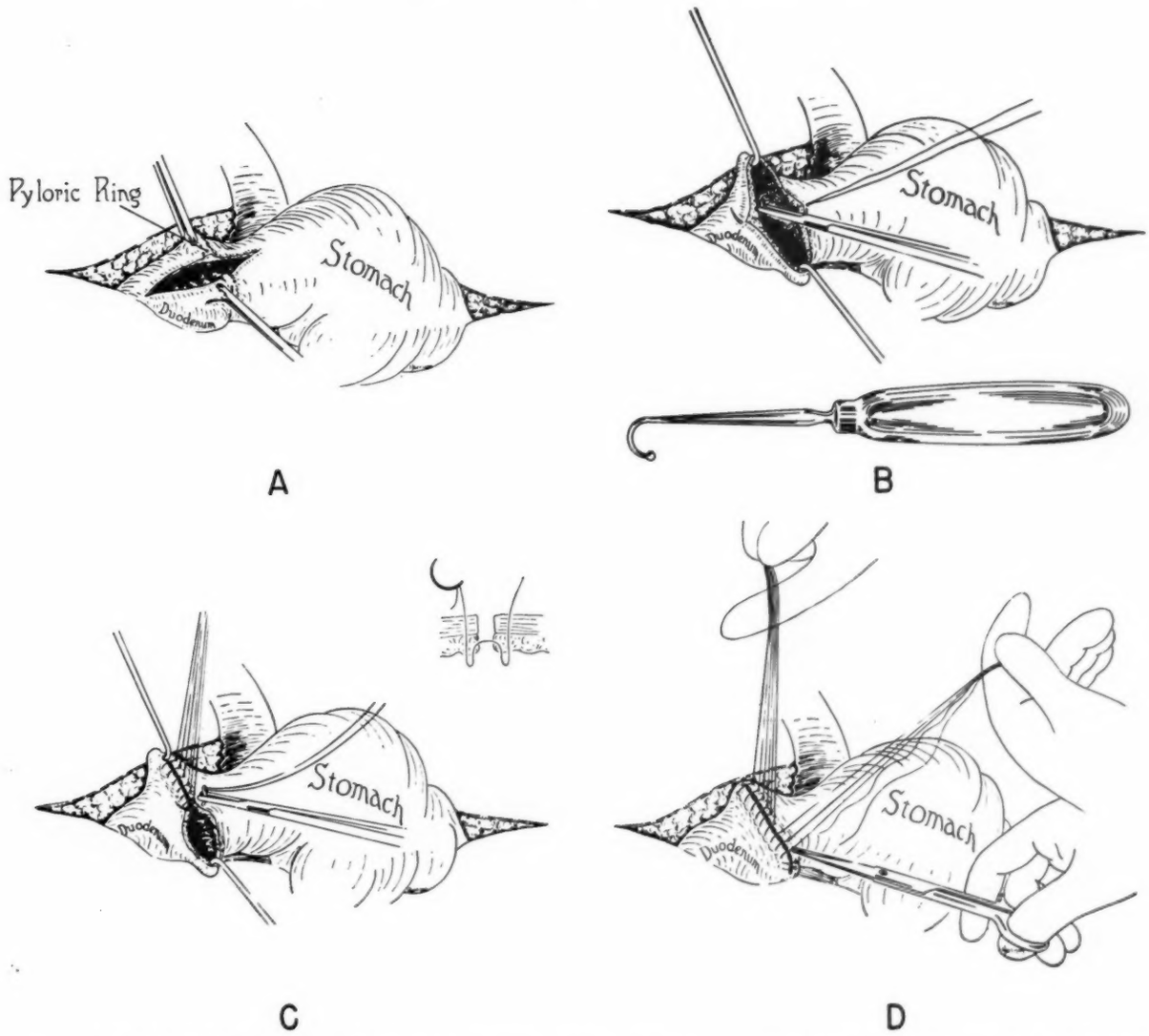


FIG. 1. Heineke-Mikulicz pyloroplasty with one-row suture technic. A, longitudinal incision across pyloric ring extending through all layers including mucosa. B, pyloroplasty retractors* convert wound by lateral traction and at the same time provide exposure for accurate placement of sutures. C, insert shows Gambee stitch which aligns mucosa to mucosa. D, completion of pyloroplasty.

on an experience with more than 900 operations of vagotomy either alone or combined with other procedures, that failure to heal the ulcer is almost invariably due to incomplete division of the vagus nerves. Good exposure is a prime requisite for successful interruption of the nerves. The esophageal hiatus is exposed by elevating the left hepatic lobe with a large bladed retractor. The peritoneum over the hiatus is then incised and the opening thus created is enlarged by finger dissection. The lower portion of the esophagus is brought into view by making traction with the index finger. Its identification is facilitated by the presence of a nasogastric suction tube within its lumen. The vagus nerves are identified and a segment is removed from each nerve at a level several centimeters above the stomach. A careful search is then made for small nerve fibers over the lower 6 cm. of the esophagus, and these are interrupted when they are found to be present. We have not found it necessary to close the incised peritoneum over the hiatus on completion of the vagotomy. There has been no symptomatic evidence of postoperative hiatal hernia in any of the more than 900 va-

* Manufactured by George P. Pilling & Son Co., Philadelphia, Pa.

gotomy operations performed in our clinic, and in only one instance has the routine postoperative barium meal x-ray examination suggested the presence of a hernia.

The pyloroplasty is performed on the principle of the Heineke-Mikulicz procedure in which a longitudinal incision is converted into a transverse one. The incision extends for a distance of at least 2 cm. on each side of the pyloric ring, passing through all layers of the ventral wall including the mucosa. The exposed mucosa is inspected for ulceration and a finger is inserted through the pyloroplasty incision down to the duodenal papilla to make certain that there is no distal constriction which would make gastroenterostomy necessary. The pyloroduodenal incision is now closed with one row of sutures according to the technic of Gambee.[8] The incised portion of the intestine is elevated by means of blunt hooks or guide sutures which at the same time make traction to convert the longitudinal wound into a transverse one. This brings all of the layers, including the mucosa, into direct view and facilitates accurate suturing. The closure is made with No. 50 cotton sutures spaced approximately 3 mm. apart. The sutures extend through all coats of the incised wall in such a manner as to approximate the edges of mucosa and the other layers without infolding the tissues. (Fig. 1C.) It is here that the stitch employed by Gambee for one-row closure is especially useful. It is important to resist the temptation to infold the tab-like projections at the lateral extremities of the converted wound. To do so might constrict the pyloroduodenal canal.

The pyloroplasty is usually performed after the vagotomy is completed. However, if the preoperative diagnosis is uncertain and there is no history of any of the complications of duodenal ulceration, the pyloroplasty is performed first in order to allow inspection of the pyloroduodenal mucosa for evidence of active or healed ulceration. If the diagnosis cannot be established, a vagotomy is not performed.

In cases of active bleeding at the time of operation or recent bleeding which appears to have subsided only temporarily, the eroded vessel is ligated by means of a deep transfixion suture immediately upon opening the pyloroduodenal canal. The pyloroplasty wound is then closed in the usual manner. If the patient's condition is extremely poor due to severe hemorrhage, the vagotomy is postponed for two weeks or thereabouts.

CONTRAINDICATIONS TO PYLOROPLASTY

Not all cases of duodenal ulcer with surgical indications are suitable for pyloroplasty. The chief contraindications to its use are: (1) excessive scarring and narrowing of the pyloroduodenal segments, (2) inflammatory edema which may be associated with acute ulceration, (3) the presence of a duodenal constriction distal to the proposed site of the pyloroplasty, and (4) the presence of a dilated, low-hanging stomach which would offer a gravitational barrier to emptying. These difficulties were not fully appreciated in our early experience, and in several instances it was necessary to perform a second operation of gastrojejunostomy or limited gastric resection because of retention. At the present time our data indicate that about one of eight cases will be unsuitable for pyloroplasty. With better recognition of the contraindications, postoperative retention is a rare occurrence.

POSTOPERATIVE MANAGEMENT

Postoperative care is an important factor in avoiding disturbing sequelae. Gastric suction by the Wangensteen method is started as soon as the patient returns to his bed, and is maintained for five days. Nothing is administered by mouth, and nutrition is given intravenously during this period. Bland liquids are given orally for two days after removal of the gastric drainage tube. Following this the patient receives a soft diet for two weeks and is then graduated to a more liberal diet which is bland in nature, and high in proteins and low in fats and carbohydrates. After several weeks the diet is not restricted. The sequelae of diarrhea, retention and "dumping" are reduced to minor considerations if this program is adhered to.

FOLLOW-UP STUDY

In order to evaluate the results of vagotomy and pyloroplasty, 200 patients with follow-up observation periods of from two to six years have been selected for study. A majority of the patients were followed up for more than three and a half years. Information concerning the results was obtained by questionnaires, personal interviews and laboratory tests.

SELECTION OF PATIENTS FOR OPERATION

A majority of operations were performed because of the complications of duodenal ulcer rather than because of intractability. It is our policy to avoid surgical treatment as much as possible in cases of intractability in which a great emotional factor is present. This is because of the generally poor results obtained with patients in this category with any type of operation. In this regard it is important to differentiate between the intractability of the penetrating ulcer and the intractability in which the manifestation of symptoms is not borne out by barium meal x-ray examinations or other objective observations. It is in this latter group that results are least likely to be satisfactory. In the 200 cases reported in this series hemorrhage, including massive hemorrhage, was the indication for operation in 43.5 per cent; intractable pain 25 per cent, obstruction 17.5 per cent, repeated ulceration 9 per cent, and inability to rule out malignancy 5 per cent.

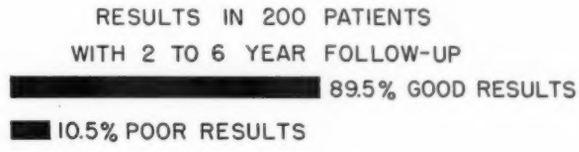
CLINICAL RESULTS

Eighty-nine and five tenths per cent of the patients have had satisfactory results. "Satisfactory" means that there is no evidence of persistence or recurrence of the ulcer and that there are no permanent disabling complications or sequelae. Most of the patients in this group expressed themselves as being very grateful for the relief which they had obtained. (Fig. 2.)

Five per cent of the 200 cases are classified as failures because of definite evidence of recurrence of ulceration (1.5 per cent) or because recurrence of ulceration could not be ruled out (3.5 per cent). In this sub-group three of the patients showed definite evidence of recurrence by direct inspection at the time of a second operation, and seven of the patients had symptoms or x-ray evidence which indicated recurrence. The insulin test gave evidence of incomplete vagotomy in five of the seven patients with suspected recurrence. A satisfactory test was not obtained in the two others.

Four per cent had poor results because of persistent disabling symptoms of retention, diarrhea or "dumping." Retention was the greatest single cause of failure in this group. Most of the instances of retention occurred before the contraindications to pyloroplasty were appreciated.

There is a remaining group of 1.5 per cent who are difficult to classify. The three patients in this group show no objective or subjective evidence of duodenal ulcer postoperatively but they are so disturbed emotionally that they cannot be said to have satisfactory results. All



ANALYSIS OF POOR RESULTS

PROVED OR SUSPECTED RECURRENCE	5.0%
DISABLING SEQUELAE	4.0%
SEVERE EMOTIONAL STRESS	1.5%

FIG. 2. Results with vagotomy and pyloroplasty.

three of these patients were described as having manifestations of severe emotional stress when they were being considered for surgical treatment. Two were operated upon because of "intractability." In retrospect, this was a poor indication and these two cases must be considered failures from the standpoint of unwise selection. The third patient was recognized as a poor candidate for surgical treatment from the standpoint of emotional tension, but an operation was deemed necessary because of repeated severe hemorrhages. This patient has had no hemorrhages in the four years since his operation.

SURGICAL MORTALITY

There have been two surgical deaths in our entire group of more than 500 operations of vagotomy and pyloroplasty. One of these was due to pulmonary embolism which occurred on the sixth postoperative day. The other, which occurred on the eighth postoperative day, was ascribed to uremia due to imbalance of electrolytes after a long preoperative period of pyloric obstruction.

SUMMARY

The aim in the surgical treatment of duodenal ulcer and its complications is to obtain permanent healing with a minimum of disturbance of the function of digestion. It is our opinion, based on a large experience over a period of six years, that vagotomy and pyloroplasty accomplish this end more effectively

than any of the other surgical procedures currently in use.

Failure to heal the ulcer by vagotomy is almost invariably due to incomplete interruption of the nerves. Complete vagotomy calls for good exposure and a familiarity with the pattern of the vagus nerves in the lower part of the mediastinum.

Special emphasis is given to the technic of pyloroplasty. The commonly used technic of employing two or more rows of sutures to close the pyloroplasty wound causes an infolding of tissues which may interfere with satisfactory emptying of the stomach and thus defeat the purpose of the pyloroplasty. This difficulty is avoided by using a single row of sutures. There has been no evidence of leakage in the more than 500 pyloroplasties performed in our clinic with the one-row suture technic.

An important consideration in the successful use of pyloroplasty is the recognition of its contraindications. It is unsatisfactory for cases in which the pyloroduodenal segment is constricted or distorted by inflammatory edema or excessive scarring. It is also unsuited for cases in which the stomach is dilated and low-hanging. Gastrojejunostomy or limited gastric resection should be used in these situations.

An evaluation of 200 patients with two to six years of follow-up study shows that 89.5 per cent have good results. Five per cent are failures because of definite or suspected evidence of recurrence. The remaining 5.5 per cent are designated as poor results for reasons of postoperative sequelae or manifestations of a disturbed emotional state.

The surgical mortality in our entire group of more than 500 operations of vagotomy and pyloroplasty is less than 0.5 per cent.

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DISCUSSION

Clarence J. Berne (Los Angeles, Calif.): I wish to compliment Dr. Weinberg and his associates on the clinical attainments that have been so well reported in this presentation. In discussing their material I would like first to emphasize that the procedure in question is vagotomy with Heineke-Mikulicz pyloroplasty. This statement may seem unnecessary but it is justified because of the very loose usage of the term "vagotomy" without sharp restriction to the exact total procedure under review. Generalizations regarding vagotomy operations are heard much too often.

Dr. Weinberg's development of the successful one-row pyloroplasty has completely eliminated early and late complications of gastrojejunostomy. This development came at a time when other surgical centers were discarding pyloroplasty because of poor drainage. The University of Southern California Surgical Service at the Los Angeles County Hospital has followed the principles but not the method recommended by Dr. Weinberg. As proof of the adequacy of these principles of gastric drainage, a survey of 150 consecutive such procedures, nearly all performed by our resident surgeons, showed only four instances of temporary stomal obstruction. Such an obstruction is an exceedingly benign situation because no duodenal content is lost, as compared to the problem with malfunctioning gastrojejunostomy. We have had no late problems with poor drainage. Further, there are very few instances of duodenal ulcer in which pyloroplasty cannot be performed.

Another technical advantage of pyloroplasty over gastroenterostomy which cannot be overemphasized is that it permits visualization of the open duodenum. This open inspection reveals those cases erroneously diagnosed as ulcer when no ulcer is present, as well as those cases diagnosed as gastric ulcer but revealed by the pylorotomy to be juxtapyloric duodenal ulcer.

The physiologic reasons favoring complementary pyloroplasty over gastroenterostomy are possibly even more important than the technical reasons. It is being recognized that poor results may follow vagotomy and gastroenterostomy unless the stoma is placed very near to, or at, the antrum. Unless this is done, two detrimental situations will de-

velop: First, as shown by Dragstedt, the poorly drained antrum is overdistended and as a result it hyperfunctions. An increase in the production of antral hormone follows, with resultant greater acidity. Secondly, as has been so well shown by Harkins and associates, the reflux of jejunal content into the stomach is a potent stimulus to acid secretion. They demonstrated that this stimulus increased progressively as the stoma was moved away from the pylorus. Both the foregoing disadvantages of gastroenterostomy are largely eliminated by pyloroplasty.

There is considerable evidence that the preservation of intact sphincter function by gastroenterostomy is objectionable. In addition to the foregoing undesirable effects above the sphincter, at least two effects occur below the sphincter. One is the jet factor. This is difficult to evaluate but it is thought to be involved with causation and localization of the ulcer, and is one possible explanation of the fact that duodenal ulcer disease presents a localized lesion instead of a diffuse one as would be expected if the acid factor alone were responsible. Less debatable is the desirability of maintaining gastroduodenal continuity, which is physiologically lost, to a large degree, with gastroenterostomy. The flow of gastric chyme into the duodenum probably stimulates acid-inhibiting mechanisms, and at least maximally utilizes the natural acid-neutralizing mechanisms. Lastly, whether because of the foregoing factors alone or because of these and the added factor of duodenal mucosal resistance, there is considerable experimental evidence that gastrojejunostomy creates a less anti-ulcerogenic situation than does gastroduodenostomy.

The foregoing technical and physiologic considerations have importantly influenced us to prefer pyloroplasty. Another advantage of the procedure is its relative safety. Our mortality rate with vagotomy and pyloroplasty at the Los Angeles County Hospital has been gratifying although not as good as the .4 per cent in the series just presented. Holman found five deaths in a study of 150 consecutive cases at the Los Angeles County Hospital. The ages of the five patients were fifty-eight, fifty-nine, seventy-seven, seventy-seven and eighty years, respectively. In the last 100 consecutive cases there has been one death, the patient being nearly seventy years of age. Possibly the most sensitive method of comparing the mortality of this procedure with that of subtotal resection is by a comparison of the results of the two procedures in the older age group of patients. In such a study at the aforementioned institution Stafford found that in the age group over sixty years the mortality for gastric resection was 10.8 per cent as compared to 4 per cent for pyloroplasty and vagotomy.

Finally, I shall comment on late postoperative results of vagotomy and pyloroplasty in two ways: First, in my personal experience only one patient has required reoperation. This was for the dumping syndrome. A reverse Heineke-Milkulicz procedure was carried out as recommended by Woodward, with good results. No such potential exists for the dumping syndrome following gastrojejunostomy. Secondly, our residents individually are allowed to choose the procedure they use for duodenal ulcer, and on the basis of their experience with the surgery and in the follow-up clinic they usually come to prefer vagotomy and pyloroplasty.

HORACE J. MCCORKLE (San Francisco, Calif.): I hesitate to discuss the paper by Dr. Weinberg and co-workers because we have had no such extensive experience with vagotomy as Dr. Berne has in Los Angeles.

Our early experiences were perhaps like those of Dr. Berne, and were rather unfavorable and led us largely to abandon this procedure for the treatment of peptic ulcer with the exception of certain selected patients who already had had partial gastrectomy and had recurrent ulcer. We are still using vagotomy for this latter type of patient.

I am afraid pyloroplasty would be impossible for most patients with peptic ulcer who are referred to our surgical services. These patients almost invariably have old, chronic, fibrosed ulcers with a good deal of inflammatory reaction and edema about the region, and would fall in the category Dr. Weinberg described as being a contraindication for his procedure.

The problem of the elderly patient with untreated peptic ulcer which requires surgery indeed may be a difficult one, and the choice between partial gastrectomy and some other type of procedure may be hard to make. I believe Dr. Bell often advocates vagotomy with gastroenterostomy in this type of patient.

Most patients with duodenal ulcer who come to our surgical service have a scarred or edematous duodenal ulcer that cannot be handled by the procedure Dr. Weinberg has described. Our choice of therapy for patients with duodenal ulcer who must have surgical treatment is partial gastrectomy.

JOSEPH A. WEINBERG (closing): I am sure that a good many feel just as Dr. Berne does that there are a number of things about gastroenterostomy that are objectionable, and that vagotomy with pyloroplasty is more of a physiologic approach than is vagotomy with gastroenterostomy.

Regarding Dr. McCorkle's comment, situations of excessive constriction or distortion of the pyloroduodenal segment are unsuitable for pyloroplasty and some other type of emptying procedure should be used with vagotomy in these cases. In our experience, most cases are suitable for pyloroplasty.

Colostomy and Ileostomy, a Simplified Technic

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THE proper function of a colostomy or ileostomy depends upon a well constructed stoma and upon training the patient in the use of this enterostomy. To secure a well constructed stoma the technic of the operation is very important. Since 1952 at the Veterans Administration Hospital, in Long Beach, California, a simplified technic for both colostomy and ileostomy has been used. The experience with these operations will be presented in this report.

In his description of a radical abdominoperineal resection Miles[7] gives a technic for the formation of a terminal colostomy. The colostomy is formed by passing the proximal colon through a muscle-splitting incision in the oblique muscles of the left lower quadrant of the abdomen. The bowel is fixed to the cutaneous wound and left to protrude beyond the surface of the skin. Variations in the technic of colostomy depend upon several factors: (1) location, (2) type of incision, (3) type of fixation to the abdominal wall, and (4) degree of protrusion of the colon. Until recently all technics for colostomy have used a segment of colon protruding above the skin surface. A variety of special clamps have been devised to hold this segment and to afford means of catheter decompression of the colon. A secondary procedure was often necessary to trim down the excess colon. The final stoma depended upon maturation of the colostomy, in which the mucosa of the colon secondarily joined the skin as the granulation tissue on the serosa contracted.

With these generally accepted ways of performing a colostomy, the rate of complications was high. Birnbaum and Ferrier[1] reviewed 569 cases of colostomy at the University of California Hospital, and 168 (or 29.5 per cent) of the cases had one or more complications. The most common complication is late stricture of the stoma. The stricture is usually at the skin level and is probably related to the protruded segment. The granulation tissue of the serosa favors edema and scar formation. Other complications of colostomy are: (1) prolapse, (2) hernia, (3) perforation or fistula, (4) necrosis or recession of the colon, and (5) small bowel obstruction due to an internal hernia between the colon and the lateral gutter.

The simplified technic for colostomy has obviated most of these complications. (Fig. 1.) The proximal colon is brought out through a separate incision in the left lower quadrant of the abdomen, usually just below or at the level of the umbilicus. The exact location is dictated by the length and blood supply of the proximal colon on completion of the resection. A 1.5 cm circle of skin is excised. The subcutaneous fat is divided but not excised. A 1.5 cm. circle of the aponeurosis of the external oblique muscle is also excised. The internal oblique and transversus abdominis muscles are split. The peritoneum and transversalis fascia are also split. The opening between the colon and lateral abdominal wall is closed with a continuous No. 00 chromic catgut stitch between the peritoneum of the colon (where it had been split lateral to the fusion fascia) and the peritoneum of the lateral abdominal wall. The colon is transected flush with the skin. The end of the colon is sutured to the skin with a continuous over and over suture of No. 00 chromic catgut, interrupted once in each quadrant.

Thirty-eight colostomies have been done with this technic. Only three complications

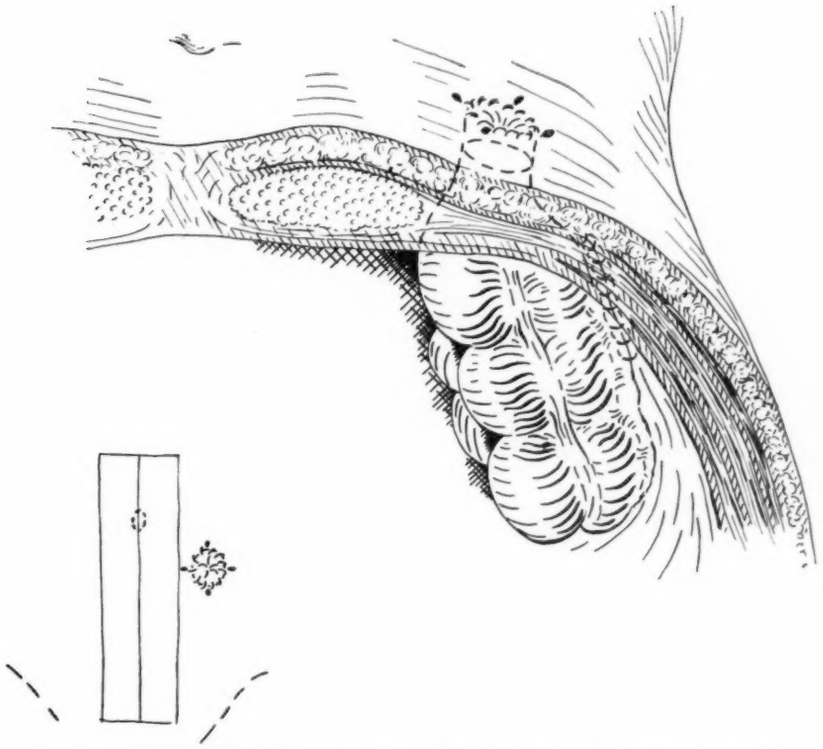

FIG. 1. Illustration of technic of colostomy. Insert shows wound dressing.

have occurred. In one case a minor infection developed about the colon; this infection cleared after the spontaneous discharge of some pus. In another case there was retraction of the colon, which caused pelvic peritonitis. Although this patient was desperately ill, he recovered with the aid of transverse colostomy and supportive care. This difficulty was due to a technical error in which the colon was brought out under too much tension. In the third complication obstruction of the small bowel occurred from an internal hernia between the colon and the lateral abdominal wall. In all of the remaining cases there was primary union between the mucosa and the skin. No secondary revision of the stoma was necessary, and no postoperative stricture of the stoma developed. With proper training the colostomies so constructed have functioned well. A bowel movement is obtained every twenty-four or forty-eight hours by means of irrigation. In the intervening periods a gauze pad, held in place by a wide elastic band, is worn.

Other surgeons have recently stressed the advantages of suturing the colon to the skin. Butler[3] uses an interrupted everting stitch, so that on completion of the colostomy " . . . the bowel wall is drawn out onto the surface of the skin while the edge is tucked under." Donald[4] has reported on the use of Butler's technic and found it very satisfactory. In our experience the use of an everting stitch is unnecessary.

Because of the success of suturing the end of the bowel to the skin in a colostomy, a similar technic was considered for ileostomy.

The more generally accepted technic for an end ileostomy is to pass the ileum through a separate stab incision in the right lower quadrant of the abdomen. The site should be situated so as not to interfere with the application of an adherent appliance. The mesentery of the proximal ileum is sutured to the peritoneum of the anterior and lateral abdominal wall. The terminal ileum is left to protrude 1½ to 3 cm. above the skin surface. As the ileostomy matures, the mucosa secondarily joins the skin. In recent years three different technics have been advocated for the management of the protruded segment of the ileum. Dragstedt[5] skin-grafted the exposed serosa. Brooks[2] everted the entire bowel wall and sutured it to the skin. Turnbull[8] excised the seromuscular layer of the exposed ileum and

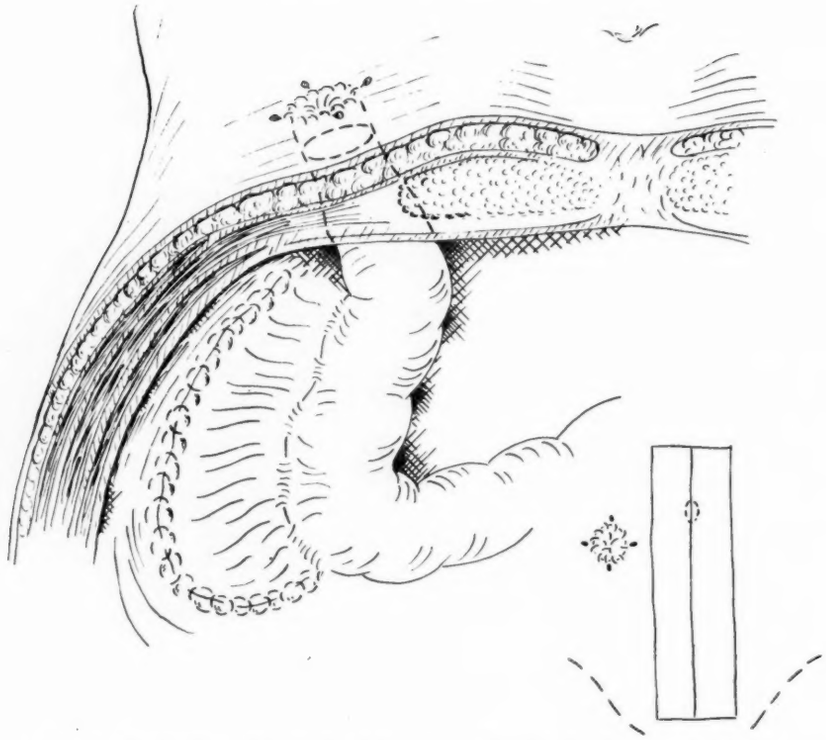

FIG. 2. Illustration of technic of ileostomy. Insert shows wound dressing.

folded the mucosa and submucosa back upon themselves.

The complications of ileostomy are frequent. Among 145 cases reported by Lyons and Garlock,[6] 32 per cent of the patients had complications and 20 per cent required reoperation for the complication. It is stated by Turnbull and Crile[8] that "Ileostomy is the main cause of complication in the surgical treatment of chronic, non-specific ulcerative colitis."

The most frequent complication of ileostomy is dysfunction. Warren and McKittrick[10] reported that 62 per cent of 210 patients had dysfunction. It is now believed that the exposed ileum contributes mainly to the cause of dysfunction, for the exposed serosa becomes inflamed and edematous, and this leads to partial obstruction. Other complications of ileostomy are: (1) prolapse, (2) fistula, (3) skin excoriation, (4) retraction, and (5) late stenosis.

The simplified technic for ileostomy has proved to be very satisfactory. (Fig. 2.) The ileum is passed through a separate incision in the right lower quadrant of the abdomen. The site is selected and marked before the operative incision, usually a midline incision, is made. The site is on a line from the anterosuperior spine to the umbilicus, far enough away from the spine so as not to interfere with the application of the ileostomy bag. A 1.5 cm. circle of skin is excised. The subcutaneous fat is divided. A 1.5 cm. circle of the fascia of the external oblique is also excised. The mesentery of the ileum is sutured to the anterior and lateral parietal peritoneum with a continuous No. 00 chromic catgut. The ileum is transected flush with the skin, and the end of the ileum is sutured to the skin with a continuous chromic No. 00 catgut, interrupted once in each quadrant. The appliance is glued into position as soon as the ileostomy begins to discharge.

Crile and Turnbull[9] have expressed the fear that suturing the ileum flush with the skin would make the application of an adherent appliance more difficult. No such difficulty has occurred in our experience. In a short time the mucosa tends to project beyond the skin to a slight degree.

Thirteen ileostomies have been done with this simplified technic, five of which were revisions of other types of ileostomies. Of these thirteen cases, three patients had moderate degrees of dysfunction. Two patients developed

prolapse, both in cases in which this technic was used to revise a previous ileostomy. The most significant fact is that eight of the patients were free of complications.

The advantage of this technic is brought out by a comparison of our ten previous cases in which the usual protruding ileostomy was made. Nine of ten patients had dysfunction. Fistulas developed in two; severe excoriation of the skin developed in one of the patients with a fistula. Five of ten patients required some secondary surgical procedure on the ileostomy.

CONCLUSIONS

A simplified technic for both colostomy and ileostomy has been presented. The main feature of this technic is the immediate suture of the bowel to the skin. The five advantages of this technic are:

1. The procedure is simple to perform and requires no special instruments.
2. It is easy to dress the stoma without grossly contaminating the operative wound.
3. Secondary surgical revision is obviated.
4. The technic significantly reduces postoperative complications, particularly dysfunction in the case of ileostomy and stomal stenosis in the case of colostomy.
5. The procedure is safe.

A well constructed stoma and proper training can make these enterostomies acceptable to the patient as a price not too big to pay for the treatment of his disease.

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DISCUSSION

Jack Mathews Farris (Los Angeles, Calif.): Most of us regard, I am sure, a well made colostomy or an ileostomy as an excellent exchange for cancer of the rectum or the ultimate fate of a patient with fulminating chronic ulcerative colitis. Numerous surgeons have modified the technics of ileostomy and colostomy in the past. The existence of these modifications indicates that none is imminently satisfactory or is a completely acceptable substitute in terms of the original model.

The fundamental point which Drs. Johnston and Movius have made is that in performing either colostomy or ileostomy the bowel must be cut flush with and sewn to the skin. This maneuver possesses an obvious advantage in that primary union occurs which as a general fundamental surgical principle is preferable to secondary healing. This technic as described by the authors is not consistent with some of the beliefs which I hold. Many of these beliefs stem from my valued association with Dr. Coller, with whom I recently had the privilege of discussing this interesting problem.

In the first place there are certain differences between ileostomy and colostomy. The fashioning of an ileostomy requires little or no interference with the blood supply of the proximal ileum and there need be little concern over viability. However, the viability of a sigmoid colostomy depends on blood which frequently arrives through collateral channels—in some instances the sigmoid colon must receive its blood from the middle colic artery. Sudek's critical point would not have received, I am sure, the attention it has if surgeons had not had an occasional unhappy experience in irrevocably predicting the viability of the proximal colon, particularly after surgical manipulation of the inferior mesenteric artery or its branches. Although most patients will tolerate ligation for example of the inferior mesenteric artery at its origin, a perusal of detailed anatomic studies indicates that the blood supply to certain left colons is precarious and meager. I, for one, would find it difficult to predict the ultimate level of viability, particularly in the obese in whom visualization of mesenteric vascular channels is difficult.

A mucosal edge which appears viable at the operating table may later become gangrenous because of stretching of the mesentery accompanying

an increase in anteroposterior diameter of the abdomen resulting from distention and increases in intra-abdominal pressure. We all agree, I am sure, that gangrene of a colostomy is a serious complication. Therefore, at the present time I am unwilling to commit myself irrevocably at the operating table as to the ultimate level of viability and prefer to exteriorize a generous segment of colon and allow it to slowly retract or revise if necessary.

From the theoretic point of view, suture of mucosa to skin is undoubtedly better, but in an occasional patient it may be unsafe. When one considers that 40 per cent of cancers of the colon and rectum are hopeless when they are first seen by the surgeon, a stricture occurring four or five years later in an occasional patient is of minor consequence.

In the consideration of strictures of colostomies I have been impressed with two features. First, the stricture is easily cured by simply excising a skin ring and then it is perfectly permissible to suture mucosa to skin as the authors advocate because the blood supply has been established. Second, I have the firm conviction that strictures of colostomies may be prevented by dilatation much the same, if one may use an analogy, as in hemorrhoidectomy where certain similar local problems exist. A number of patients with stricture of the colostomy have either failed to carry out dilatations or were not instructed to do so in the first place.

I am certain the fiberoserositis, on the other hand, occurring in an exteriorized loop of ileum, is responsible for many instances of malfunction. It seems to me that the method as described by the authors has certain advantages over exteriorizing large segments of ileum. I would have no hesitancy in applying this method.

Progress in surgery can be achieved only through studies such as these, and I hasten to assure Drs. Johnson and Movius that any difference of opinion I have expressed is simply a friendly difference in point of view, without which I am sure you will agree these meetings and discussions would no longer exist.

ROBERT A. SCARBOROUGH (San Francisco, Calif.): I enjoyed the paper by Drs. Johnston and Movius very much because we have gone through the problems of trying to improve our technic particularly of ileostomy, having recognized that ileostomy dysfunction was the major complication of surgery for ulcerative colitis.

I certainly want to endorse the principle of a simple, primary open anastomosis of the end of the ileum to the skin in the formation of an ileostomy. We have done this in a number of patients. When Crile and Turnbull described their technic, we adopted it. We treated about ten patients with the technic and found that in approximately 50 per cent of the patients it was done quickly and easily but in the remaining patients it was difficult to strip off the muscularis and serosa. We have gone back to the simple technic described by Drs. Johnston and Movius.

You do not need a spigot of bowel sticking out beyond the abdominal wall in order to apply a modern ileostomy bag which is cemented to the skin. By this technic we have avoided dysfunction and have had no complications. However, I agree with Dr. Farris that there are hazards in the formation of the colostomy. There are problems which do not warrant routine adoption of this technic in the formation of a colostomy where a wide, radical type of resection has been performed for carcinoma of the rectum or rectosigmoid and the arc of resection has included not only the superior hemorrhoidal vessels but also all the sigmoid vessels and often the left colic artery, so that there is a definite diminution in the blood supply to the descending colon that is used to form a colostomy. It depends on the blood supply which comes from the marginal artery. This supply is adequate in most cases, fortunately; however, we have used this technic in colostomy at times thinking there was a good blood supply and have been most distressed to find necrosis of all visible bowel in twenty-four or forty-eight hours. Fortunately, such necrosis has not extended into the peritoneal cavity but has resulted in an extensive area of breakdown of tissue with a serious complicating stricture which requires major revision for the formation of a competent colostomy.

I think the technic of simply bringing an extra few centimeters of colon to the outside is adequate in colostomy. We do not have the immediate dysfunction with the colostomy that we have with an ileostomy performed in the same manner, because in the colon mass peristalsis can propel the fecal content beyond the area of serosal peritonitis and functional obstruction and there is no obstruction.

It is true that in a certain percentage of these patients late strictures will develop after three, five, ten, fifteen or twenty years. However, it is also true that those strictures are simply repaired by making three radiating incisions through the stenotic scar tissue ring at the mucocutaneous junction. We have done that with four patients in the last month, hospitalizing them for twenty-four hours. Healing is prompt and the patients do well thereafter.

PAUL W. JOHNSTON (closing): I appreciate very much the endorsement of this technic for ileostomy given us by Drs. Farris and Scarborough. I must admit that we had more fear in applying this method to ileostomy than in applying it to colostomy.

In all our experience we have had no difficulty with the blood supply of the distal colon. In per-

forming resections of the left colon and abdominoperineal resections, we have routinely transected the inferior mesenteric artery at its origin in order to remove the maximum amount of lymph node–bearing tissue, and have depended upon the marginal artery of Drummond for the blood supply of the distal colon. However, we inspect the colostomy six to eight hours after the procedure to make sure that the mucosa of the colostomy is viable.

I do not believe you can judge the blood supply of the protruded segment as being an indication of what will happen to the distal colon by this technic, for vessels in the exposed segment are much more likely to thrombose than the vessels which are in the peritoneal cavity.

Lipomatosis of the Ileocecal Region

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LIPOMATOSIS of the ileocecal region, also called the ileocecal valve syndrome and the pouting ileum, is an infrequent pathologic entity. Its chief interest lies in the fact that it may give rise to exsanguinating hemorrhages.

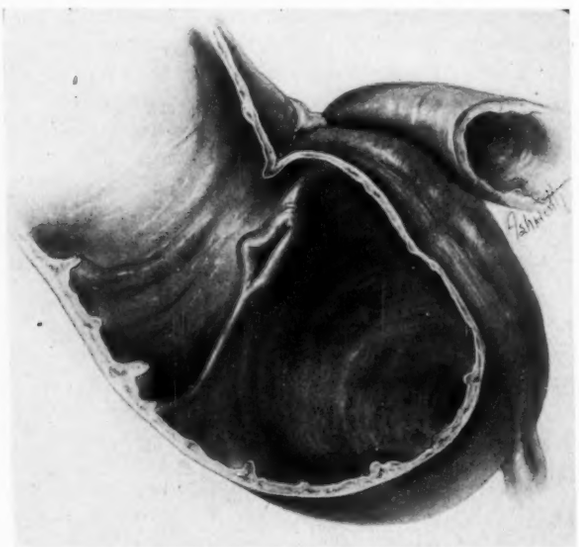

FIG. 1. Normal ileocecal valve.

According to Lasser and Rigler,[1] the condition is characterized by abdominal distention and pain in the right side of the abdomen, by tenderness on palpation and by fluoroscopic evidence of enlargement of the ileocecal valve. Hinkel[2] attributed the characteristic enlargement of the ileocecal valve to prolapse of the ileal mucosa, edema of the mucosa, polyps, carcinoma and accumulations of fat in the submucosa.

Normally the ileocecal valve enters the cecum at a right angle and projects into it as a papillary prominence. (Fig. 1.) The bluntly ending ileal walls, called the upper and lower lips, form the valve proper. Studying the ileocecal valves at fifty consecutive autopsies, Fleischner and Bernstein[3] noted that while there was great variability in the thickness of the lips, most of them measured from 0.3 to 0.5 cm. The increased thickness of the lips was almost always due to accumulation of submucosal fat. Zettergren[4] studied the ileocecal valves of forty-three adults who had died from diseases of the heart and vessels. He likewise noted considerable variation in the thickness of the lips which was due to accumulations of fat, ranging from only a few isolated groups of fat cells to a well developed ring of submucosal fat. He noted, further, that there seemed to be a direct correlation between the amount of fat deposited in the bowel mesentery and the amount in the ileocecal valve.

The radiologic literature contains frequent references to enlargement of the ileocecal valve. Golden[5] is credited with first calling attention to this abnormality. Rigler and Lasser[6] pointed out that the condition is found more often when it is borne in mind. Lewis and Mueller[7] stated that after they started looking for enlarged ileocecal valves they found as many as ten in one year.

In spite of the growing awareness of this condition, little has been done to correlate the clinical findings. Lasser and Rigler[6] recently reviewed the findings in eighteen patients in whom this condition had been observed on barium examination. They noted that all the patients had a common symptom complex, namely, vague abdominal pain and distention as well as tenderness over the cecal area. Pathologic proof of the cause of the enlarged valve is lacking in their series.

Our interest in this problem was stimulated

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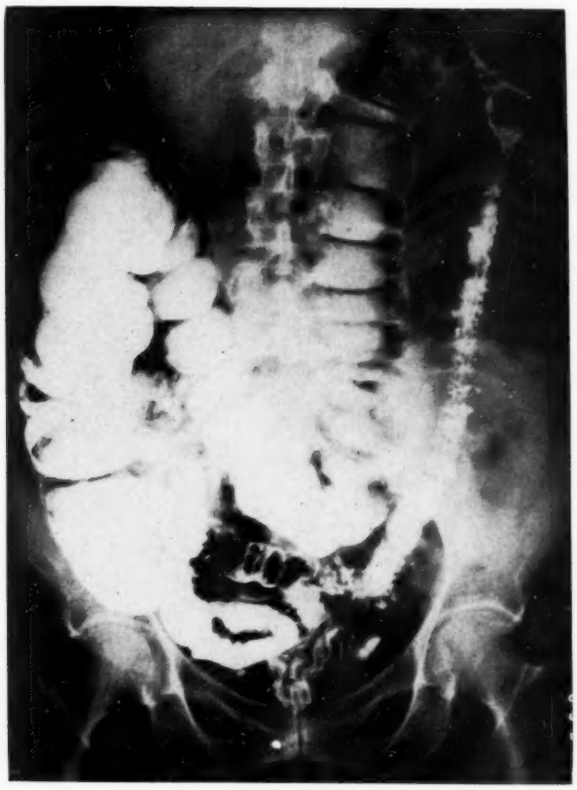

FIG. 2. Case 1. Barium enema; September, 1954.

by three patients treated in St. Vincent's Hospital.*

CASE REPORTS

CASE 1. J. S., a sixty-eight year old woman, entered the hospital in September, 1954, because of recurrent bleeding per rectum.

In 1928 she had had a gastroenterostomy for peptic ulcer. Following this operation she was in good health except for hypertensive heart disease. In December, 1949, she passed bright red blood per rectum. The bleeding recurred repeatedly. On occasions exsanguination was so great that blood transfusions were necessary. Barium enema in 1949 disclosed only multiple diverticula of the sigmoid colon.

Roentgen studies were repeated in September, 1954, and again showed only the sigmoid diverticulosis. The cecal area was reported as being normal. (Fig. 2.) Sigmoidoscopic examinations failed to show any bleeding site.

It was decided to resect the sigmoid colon in the hope that this might be the site of the hemorrhage. Since the red blood count was 3.2 million per cu.

* We are grateful to Dr. Russell Johnsrude and Dr. E. W. St. Pierre who furnished us with the histories and laboratory findings for their respective patients. The third patient was operated on by one of us (D. B. S.).

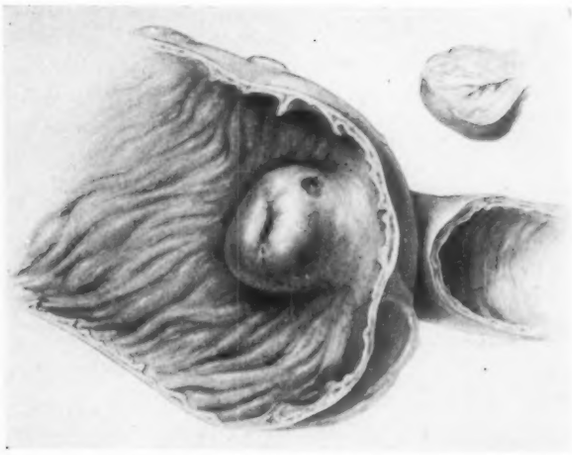

FIG. 3. Case 1. Lipomatosis of valve. Note small bleeding ulcer.

mm. and the hemoglobin 8.9 gm. per cent, she was given 1,500 cc. of whole blood prior to operation. Through a lower left rectus incision, the sigmoid colon was resected. The entire colon was carefully inspected and palpated. Except for multiple diverticula, no abnormality was found. Pathologic examination of the resected bowel revealed no definite bleeding point.

The patient did well until the evening of the sixth postoperative day when she complained of feeling faint. About an hour and a half later she passed a large quantity of dark blood by rectum. An hour after this she passed another large amount of dark blood. Following this she went into shock.

Transfusions of whole blood were started while she was being taken to surgery. The abdomen was reopened through the previously made incision. Repeated palpation of the entire length of the colon elicited only a "slight thickened feeling" in the cecum. An incision was made over the thickened cecum, and a "pouting" ileum was observed. It was somewhat yellowish in color and had the appearance of diffuse lipomatosis. Blood was pouring from a tiny ulcer on this projection. (Fig. 3.)

The terminal ileum and ascending colon were resected and end-to-end ileotransversostomy was performed. The pathologic diagnosis was "lipomatosis of the submucosa of the terminal ileum with prolapse and low grade chronic inflammation and edema." (Fig. 4 and 5.)

CASE II. S. W., a fifty-nine year old woman, was admitted to the hospital on November 22, 1953.

She had been in good health until 1945 when she became constipated and complained of abdominal distention. In 1949 she lost weight and noted tarry stools for the first time. Subsequently she lost so much blood in this manner that she had several

FIG. 4. Case 1. Photomicrograph through lipomatous ileocecal valve showing fatty infiltration.

fainting spells. The melena persisted intermittently for two years despite medical treatment. In 1951 roentgen studies revealed a duodenal ulcer and a filling defect in the cecum. (Fig. 6.) Under medical management the ulcer improved so that at re-examination in 1953 it could no longer be demonstrated. In October of that year barium enema was followed by passage of bright red blood per rectum. After fainting on the street she was hospitalized.

Physical examination was normal except for pallor and moderate distention of the abdomen. In spite of her bleeding, blood pressure was 140 systolic and 98 diastolic. Red blood count was 3.46 million per cu. mm.; hemoglobin was 8.83 gm. per cent. The preoperative diagnosis was carcinoma of the cecum.

At operation the surgeon noted that "within the cecum was palpated a soft, polypoid mass." Except for numerous diverticula of the sigmoid the rest of the abdomen presented no abnormality. The terminal ileum and the ascending colon were resected, after which side-to-side ileotransversostomy was performed. Pathologic diagnosis was herniation of the mucosa of the small bowel through the ileocecal valve, apparently due to submucosal lipoma with superficial erosion of the mucosa. (Fig. 7.)

CASE III. M. F., a sixty-five year old woman, was admitted to the hospital on July 28, 1954.

She had been in good health until March, 1954, when she noted fatigability, weakness and dyspnea on exertion. A blood count disclosed anemia for which she was given iron and multivitamins. Later she complained of paraumbilical pain, anorexia and shakiness. She had had black stools, but had passed no bright red blood per rectum. No other change in bowel habits had been noted. In the six months prior to admission the patient had lost 10 pounds.

Roentgen study showed a filling defect in the cecum near the ileocecal valve. (Fig. 8.)

Physical examination was normal. Blood pres-

FIG. 5. Case 1. Photomicrograph through another portion of ileocecal valve. Note fatty infiltration.

sure, despite the bleeding, was 190 systolic and 80 diastolic. The red blood count was 4.85 million per cu. mm. and hemoglobin was 12.97 gm. per cent. The preoperative diagnosis was large polyp of the cecum.

On exploration, the surgeon palpated a soft, polypoid mass in the cecum. Opening of the cecum disclosed prolapse with induration and ulceration of the mucosa of the terminal ileum into the cecum. After preliminary cecostomy, the terminal ileum and ascending colon were resected and end-to-end ileotransversostomy was performed. Pathologic diagnosis was "prolapse of the ileal mucosa through the ileocecal valve, secondary to submucosal lipomatosis." (Fig. 9.)

COMMENTS

Review of the literature revealed twenty-one cases of lipomatous enlargement of the ileocecal valve. Nine are not included in the present analysis. In five cases the enlargement was found incidentally at autopsy.[8,9] In four the enlargement of the ileocecal valve was an incidental finding at the time right colectomy was done for the following conditions: persistent cutaneous fecal fistula after appendectomy,[10] enteritis,[11] and carcinoma of the hepatic flexure in two instances.[3,4]

The remaining twelve cases [1,4,6–8,10,12–16] and our three make a total of fifteen which were evaluated. Analysis of these corroborates the observations reported by Lasser and Rigler.[1] Of the fifteen patients, twelve were women. Only two of the fifteen patients were less than forty-five years old: one was a woman aged thirty, the other a man aged forty-one. The remaining thirteen patients were between fifty-one and seventy years old, eleven being women and two men. With one exception, the bleeding occurred in patients of this age group.

Nine patients had had symptoms for one year or less before surgical relief was sought.

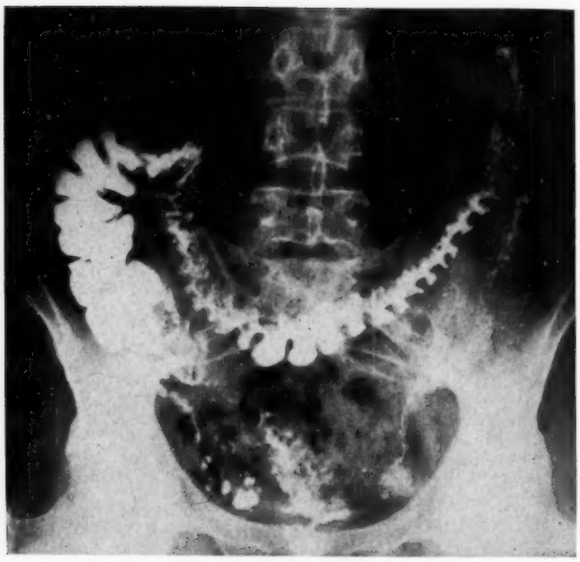

FIG. 6. Case II. Filling defect in cecum.

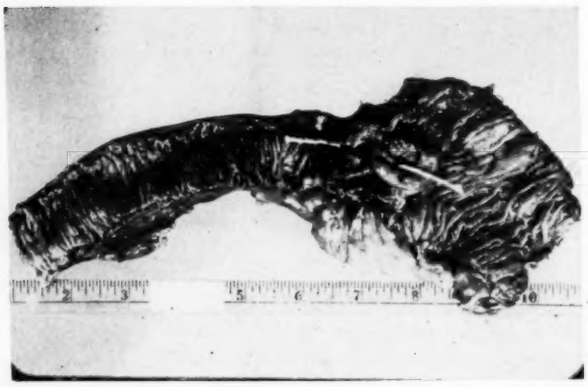

FIG. 7. Case II. Lipomatosis of ileocecal valve with erosion of mucosa.

FIG. 8. Case III. Roentgenogram localized to cecum. Note filling defect.

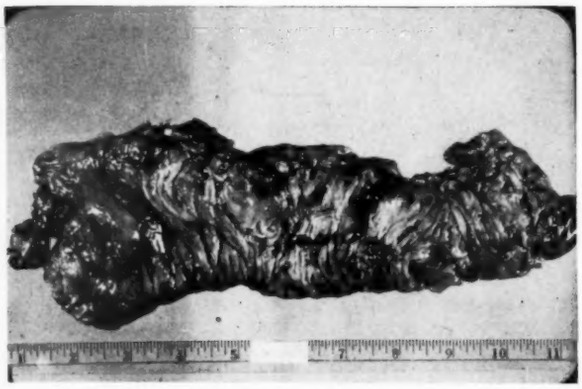

FIG. 9. Case III. Lipomatosis of ileocecal valve with superficial erosion.

The others had had symptoms for from three to as many as six years.

Twelve patients had abdominal pain ranging from mild to severe. In seven patients the pain was localized: in the epigastrium, one; in the paraumbilical region, two; in the lower right quadrant, two; in the hypogastric region, two. In five patients the pain was not localized.

The next most frequent symptom was bowel dysfunction which occurred in eight patients. Constipation was common. However, some patients had diarrhea and others excessive flatulence.

Passage of bright red blood per rectum or melena, or both, occurred in seven patients. Indeed, it was this facet of the problem that interested us most. Surprisingly little is said in the literature relative to bleeding per rectum as a result of an enlarged ileocecal valve.

A palpable mass was present in only three patients. In two of these tenderness was elicited.

The enlarged valve probably causes mechanical changes in the bowel which lead to irregular and forceful peristalsis, obstruction, intussusception and ulceration with bleeding.[8,17] In six of the seven patients who bled, the valvular mucosa revealed superficial erosion as well as areas of mucosal hemorrhage with necrosis, inflammation and ulceration.

On palpation through the cecal wall the in-

volved valve had a characteristically soft, lobulated feeling. When examined *in situ*, the appearance of the valve was the same as noted by Edwards and Zangara[15] and also by Zettergren[4] who aptly described it as resembling a "boggy cervix protruding into the vagina."

Although closely related to the frequently reported lipomas of the ileum and cecum,[11,13,17–19,21–23] lipomatous enlargement of the ileocecal valve is not identical and presents a special problem. In our opinion, operation is indicated when roentgen examination discloses a filling defect in the ileocecal valve area of a patient who has had abdominal pain, bowel dysfunction and, especially bleeding per rectum. Right colectomy is the treatment of choice.

SUMMARY

Three new cases of lipomatosis of the ileocecal valve are reported and twelve cases from the literature are reviewed. In all fifteen patients definitive operations were performed. Nine other cases found in the literature were excluded because the condition was found incidentally at autopsy or at operation for other problems.

In seven of the fifteen patients severe bleeding per rectum was a symptom. Therefore, if rectal bleeding persists from an undetermined site, the possibility of lipomatosis of the ileocecal valve should be kept in mind. Roentgenograms localized to the ilecoecal region should be made to see if there is the characteristic enlargement of the valve. The treatment of choice is right colectomy.

ADDENDUM

Since this paper was presented before the Association (February, 1956), three more instances of this condition have been reported to the senior author. The first communication came from Dr. Frederic P. Shidler of Menlo Park, California. A few days after hearing this paper he operated upon a patient with a history of severe and repeated hemorrhage from the large bowel. Exploration revealed no apparent cause. Finally, remembering this paper, he opened the cecum and found a typical lesion of lipomatosis of the ileocecal valve with prolapse and hemorrhage. The second case was that of Dr. Allen Boyden of Portland, Oregon, a discussor of this paper. He called the senior author into his surgery and demonstrated a perfect example of this lesion. His patient also had had severe and recurrent hemorrhages. The third case was that of Dr. Joseph M. Roberts of Portland, who diagnosed this condition from radiographic studies of the cecum. His patient had not bled but had recurrent cramp-like pain in the lower right quadrant.

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DISCUSSION

Allen M. Boyden (Portland, Ore.): A patient who came under my care at the U. S. Veteran's Hospital early in 1948 had an unusual case of massive exsanguinating intestinal hemorrhage. This sixty-nine year old man was transferred to the surgical service on December 2, 1947, because of passage of bloody stools of one week's duration. He had been hospitalized originally for treatment of urinary infection associated with diverticula of the bladder. The pertinent physical findings included obesity, blood pressure of 160/80, protuberant nontender abdomen and dark blood on the gloved finger at rectal examination. The red blood cell count was 4.3 million per cu. mm. Hemoglobin was 81 per cent. Bleeding and coagulation times were within normal limits. Blood urea nitrogen was 18.9 mg. per cent.

Repeated double contrast barium enema studies revealed moderate diverticulosis of the sigmoid with a questionable smooth, circular defect at the ileocecal junction.

At sigmoidoscopy a small polyp was removed at 15 cm. It showed an area of focal carcinoma *in situ*.

The patient had no further episodes of bleeding until January 16, 1948 (six weeks later), when he passed a moderate quantity of dark bloody stool accompanied by mild abdominal cramps. Repeat barium enema yielded similar findings to those previously noted, the size of the ileocecal defect varying according to the degree of contraction of the cecum itself.

At abdominal exploration on February 5th (three weeks after the patient's last hemorrhage) no abnormalities were found. Despite the absence of palpable abnormalities, the cecum was opened. The ileocecal valve was represented by a large pouting ring which was at first throught to be a submucosal lipoma, but on closer inspection seemed to be merely redundant ileal mucosa with excess fatty deposit in the submucosa. Since no ulcerating area was present and since we were unaware of the possibility of severe hemorrhage from such an innocuous-appearing abnormality, the colon was not resected. The cecum was closed and the appendix was removed. Uneventful convalescence permitted the patient's discharge on the twenty-third postoperative day.

He was readmitted on March 8th (eight days later) having passed four bloody stools the day of admission, preceded by low abdominal cramps. He was pale and apprehensive. Blood pressure was 130/80. The hemoglobin was 65 per cent and the red cell count was 3.55 million per cu. mm. I quote from the report of the radiologist after barium enema: "The terminal ileum and ileocecal region are clearly demonstrated on the original fillup films. One can see the rugal folds of the terminal ileum entering the cecum in a perfectly normal manner. However, on the postevacuation study it is interesting to note that after the patient strained and bore down in evacuating a large quantity of barium, the defect in the cecum is due to a prolapse of the ileal mucosa, a small gap of about ½ inch occurring between the junction and the head of the barium column in the ileum. In other words, it is clearly demonstrated that prolapse has again occurred after evacuation, that there is a freely prolapsing and reducing mucosa, and, consequently, that the mucosa is subjected to the trauma of this phenomenon." Review of the literature yielded no instance of hemorrhage from such a prolapsing ileocecal valve.

On March 22, 1948 (fourteen days after the last hemorrhage), thorough abdominal exploration was again carried out. Palpation and inspection of the cecum and ileocecal junction revealed no abnormality. Right colectomy with ileotransversostomy was elected because of the persistent roentgen abnormality in the ileocecal region. During the course of the manipulation necessary to free the cecum and ascending colon it was noted that the cecum became filled with blood, and after its removal this was found to have come from petechial areas in the prolapsed ileal mucosa. There was no point of true ulceration. The submucosa appeared to contain considerable fat.

Microscopic sections revealed no mucosal ulceration. The submucosa was extremely fatty, but otherwise showed no change except for one minute focus of inflammatory infiltration.

The patient's convalescence was uneventful except for a superficial wound infection. He was discharged on the twentieth postoperative day. Follow-up examination almost eight years later revealed him to be in good health. There had been no further episodes of intestinal bleeding.

This case makes an interesting addition to the three cases reported by Dr. Seabrook and his co-authors. The demonstration by roentgen examination of prolapse of the mucosa of the ileum through the ileocecal valve would seem to prove that this repeated trauma is the major factor in the pathogenesis of hemorrhage from this lesion. Excessive fatty deposition in the submucosal layers of the terminal ileum is the apparent cause of the prolapse.

Alois E. Moore (San Diego, Calif.): In 1954

I was confronted with a similar problem, except for the hemorrhage. A sixty year old white woman complained of pain in the right lower quadrant, and a tumor filling defect was found on x-ray examination. The radiologists suspicioned that this was a polyp. At operation it was almost undetectable and certainly was not a malignant disease clinically. Consequently, the cecum was opened and the yellow doughnut described so well by Dr. Seabrook was inspected, and as Dr. Boyden said, resembled a lipoma. On more careful digital examination through the ileocecal valve, it was obvious that a heavy deposit of fat was located in the submucosa. This patient had no hemorrhage.

We debated about the treatment for this patient. It was believed that resection of the right colon was a little too radical a procedure for what was obviously a benign lesion. Circumcision of the ileocecal valve was performed (which is not difficult to do), incising down one side and following the circumcision with a lock stich of catgut. The patient has remained perfectly well since the operation.

ROBERT A. SCARBOROUGH (San Francisco, Calif.): I have experienced two such cases in the past, and again diagnosed this condition in two patients in recent months.

I would like to call your attention to the fact that differential diagnosis is sometimes difficult, and there are other and even more serious conditions which may resemble lipomatosis of the ileocecal valve. The following two examples prove this point: A spot film of the cecum of a patient was mistakenly diagnosed as lipomatosis of the ileocecal valve. This proved to be lymphosarcoma of the ileum intussuscepted through the ileocecal valve. In another patient the spot film, which was quite similar in appearance to the first, was also misdiagnosed as lipomatosis of the ileocecal valve. The patient actually had annular adenocarcinoma of the ileocecal valve.

DEAN B. SEABROOK (closing): Lipomatosis of the ileocecal region is like any other rarity; when it is mentioned, other physicians cite similar cases. I am astounded that Dr. Scarborough diagnosed this condition. I think it is wonderful that anyone has advanced that far. I did not know this condition existed and for this reason I was uncertain the first time and almost lost the patient. It was extremely interesting to me that after operating for thirty-two years I could discover something I had never heard of before.

Dr. Boyden's remarkable case parallels our own experience exactly. The fact that his patient bled emphasizes our contention that hemorrhage may be the most alarming symptom of this entity.

Ten Years' Experience with a Single Layer Anastomosis in Colon Surgery

LOUIS P. GAMBEE, M.D., WILLIAM GARNJOBST, M.D. AND CLIFFORD E. HARDWICK, M.D.,
Portland, Oregon

TEN years ago a single layer open technic for intestinal anastomosis was described by Gambee.* This initial description had been preceded by an experience of several years during which a favorable impression had been gained through its employment in nearly all forms of large and small bowel anastomosis. The purpose of this present paper is to describe our subsequent experience with the technic, mainly to determine, if possible, whether the original confidence in it has been vindicated. This study is also motivated partly by our conviction that those who describe innovations in surgery are obliged to make known their eventual results.

THE TECHNIC

The technic has not been altered basically from the original description. It consists simply of an interrupted, inverting suturing of the full thickness of the bowel walls, using a single row of non-absorbable sutures of either cotton or silk. (Fig. 1.) Prior to beginning the anastomosis, the fecal stream is controlled by heavy occlusive ligatures tied around the intestine several inches from the divided ends. Since these ligatures do not compress the mesenteric vessels, as rubber-shod clamps might, they afford the added safety of avoiding possible injury to the mesenteric vessels and allow continuous assessment of the vascular adequacy after division of the bowel. They also allow manipulation of the ends with a minimum of trauma. The posterior halves of the intestinal circumferences are sutured from within the lumen, inversion of the walls being supplied by slight tension on the lateral guy sutures. The remaining half of the anastomosis is completed by interrupted inverting sutures placed as shown in Figure 2. Additional sutures are added whenever necessary to provide adequate inversion and sealing.

TABLE 1

Site of Resection	Indication for Resection	
Right colon (36)	Carcinoma	31
	Ulcerative colitis	3
	Volvulus	1
	Other	1
Transverse and splenic flexure (31)	Carcinoma	11
	Colostomy	19
	Volvulus	1
Descending and sigmoid colon (96)	Carcinoma	68
	Diverticulitis	21
	Volvulus	2
	Endometriosis	1
	Megacolon	1
	Stenosis	1
	Colostomy	1
	Factitial colitis	1

The foremost advantage of this method of anastomosis has been its simplicity and ease of performance, even under relatively adverse conditions. It has been of particular value in joining bowel ends unequal in diameter. One might expect that there would be less hazard of obstruction since the single layer results in a narrow flange of turned-in tissue. Furthermore, a single row of sutures would be expected to produce minimal disturbance in the blood flow to the healing area.

* Read before the Pacific Coast Surgical Association, San Francisco, California, February 20, 1946. (Published: GAMBEE, L. P. A single-layer open intestinal anastomosis applicable to the small as well as the large intestine. *West. J. Surg.*, 59: 1–5, 1951.)

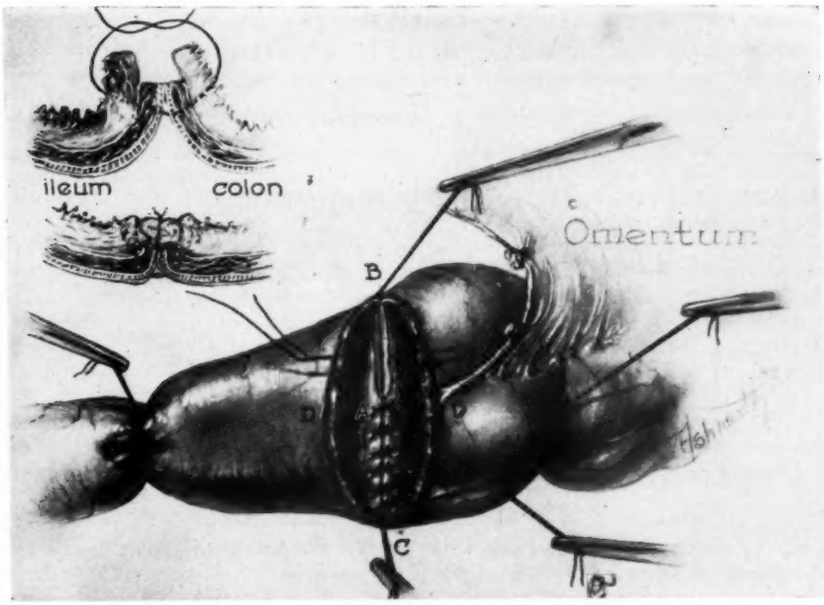

FIG. 1. The sutures in the first half of the anastomosis are placed from within the lumen, as shown. Slight tension on guy sutures (B and C) facilitate inversion of the edges. The proximal and distal occlusive ligatures are placed before dividing the bowel.

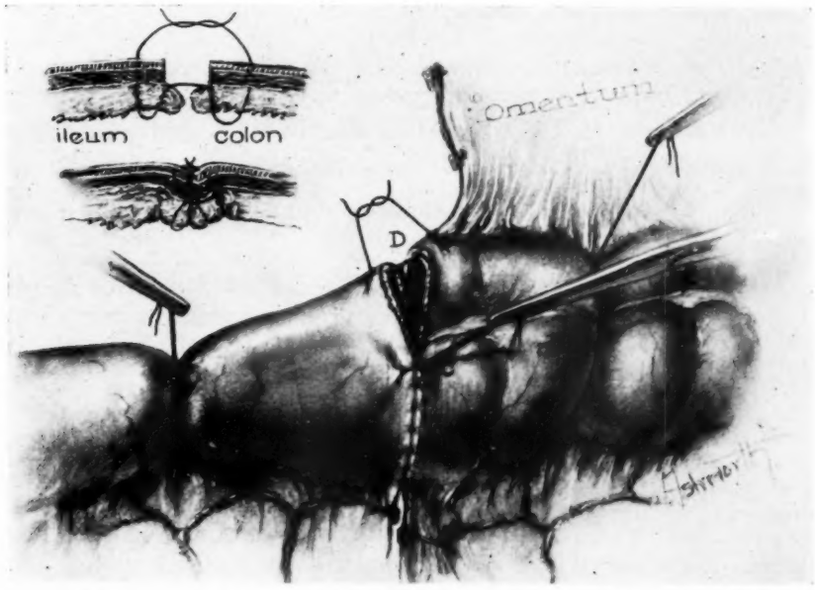

FIG. 2. The anastomosis is completed by interrupted inverting sutures, placed as shown.

The technic has been applied to anastomoses in both the large and the small intestine, including cholecystojejunal, gastroduodenal and esophageal anastomoses. Those anastomoses performed in the colon have comprised the largest group numerically, and it is for this reason that they have been selected as a basis for this report. As indicated in Table 1, 163 large bowel anastomoses were performed after resection for various indications. The series consists of consecutive cases during a period in which all colic anastomoses were performed by the described technic.

Fatal Anastomotic Complications. There were

TABLE II
FATAL ANASTOMOTIC COMPLICATIONS

Case No.	Procedure	Complications	Factors Present at Surgery
14L	Left colectomy for carcinoma of sigmoid; small bowel resection	Leak with pelvic abscess	Multiple fistulas between sigmoid and small bowel
94L	Sigmoid resection for diverticulitis	Leak with pelvic abscess; fistulas	Partial obstruction; active infection
65L	Sigmoid resection for diverticulitis; resection of involved ileum	Leak with fecal fistula; small bowel obstruction 1 mo. later due to adhesions and small abscesses	Multiple small pelvic abscesses involving ileum
22C	Right colectomy for carcinoma of cecum	Leak with peritonitis	Nearly complete obstruction
14L	Rectosigmoidectomy for carcinoma (anastomosis below reflection)	Leak with pelvic and perirectal abscess	None

TABLE III
NON-FATAL ANASTOMOTIC COMPLICATIONS

Case No.	Procedure	Complications	Factors Present at Surgery
31M	Left colectomy for idiopathic megacolon	Leak with pelvic abscess; subsequent stenosis	Marked disproportion; intraluminal mercury
93L	Sigmoid resection for diverticulitis	Leak with pelvic abscess	Partial obstruction; small abscess
12M	Right colectomy for carcinoma	Fecal fistula	None
1C	Sigmoid resection for carcinoma; transverse colostomy (anastomosis below reflection)	Small leak found on barium enema	None
18C	Sigmoid resection for diverticulitis; transverse colostomy	Small leak found on barium enema	None
89L	Right colectomy for carcinoma	Small leak found on barium enema	Nearly complete obstruction
24L	Left colectomy for carcinoma	Asymptomatic stenosis found on barium enema	None
37C	Sigmoid resection for diverticulitis	Postoperative obstruction requiring colostomy	None
12C	Right colectomy for ulcerative colitis	Postoperative obstruction requiring ileostomy	Disease at level of anastomosis

five fatalities due directly or indirectly to anastomotic failure with leak.* From Table II it can be seen that four of these five cases presented rather formidable difficulties before surgery. It is apparent that in the first three cases listed, primary anastomosis without proximal colostomy imposed too severe a test of the sigmoid anastomoses and, therefore, should probably be considered primarily as surgical errors. The ileocolic anastomosis in the fourth patient was compromised from the beginning by inability to achieve adequate decompression of the small bowel after five days of long tube suction. In the last of these five patients the anastomosis, which was below the peritoneal reflection after palliative resection, broke down in the absence of pre-existing complicating factors and can be properly considered a true anastomotic failure.

Non-fatal Anastomotic Complications. Non-fatal complications included six anastomotic leaks, three of which were major, resulting in either intraperitoneal abscess or fecal fistula; the remaining three consisted of small walled-off cavities discovered on postoperative barium enemas. (Table III.) One of the major leaks occurred in an adult with congenital megacolon in whom a huge dilated segment of transverse colon was pleated into a very much smaller distal bowel low in the pelvis. To compound this, free intraluminal mercury from a Miller-Abbott balloon lodged in the anastomotic line. The perforation which ensued persisted for many months as a chronic granulomatous cavity, necessitating later revision of the anastomosis. It is doubtful that any form of anastomosis would have survived this test. One of the remaining two major leaks occurred in an anastomosis performed after resection for diverticulitis in the presence of a small intraperitoneal abscess. The other major leak, a small temporary fecal fistula following right colectomy (Case 24L), occurred in the absence of preexisting complications and must be considered as a pure anastomotic failure.

A single instance of partial stenosis in an otherwise uncomplicated course was discovered inadvertently on a routine barium study two months after sigmoid resection for carcinoma. Although the narrowing produced no symptoms, the area was explored because the defect suggested persistence of tumor.

As had been hoped, the incidence of postoperative obstruction at the suture line was low, occurring in only two patients. Both followed resection for inflammatory disease, namely, diverticulitis of the sigmoid and segmental ulcerative colitis of the right colon. The obstruction in the latter case was explained in part, at least, by the finding of active disease at the level of distal resection.

One might ask whether any late complications occurred as a result of placing non-absorbable sutures into the intestinal lumen. We have observed several instances of small granulomas about sutures in anastomoses low in the pelvis, but elsewhere in the colon we have been impressed with how little reaction may be present around sutures which have been in contact with the lumen for years.

* Eight other postoperative deaths occurred in the series. Five autopsies were performed, revealing the anastomosis to be intact and patent. In the remaining three cases there was no clinical suspicion of anastomotic complication.

SUMMARY

In summary, five fatalities due to anastomotic complications were encountered in a series of 153 anastomoses, with a resulting mortality incidence of 3 per cent; the incidence of all types of anastomotic complications was 8.6 per cent. The latter group included a considerable proportion of defects which were asymptomatic and found incidentally in postoperative barium studies. Unfortunately these figures cannot be compared statistically with other series because of the diversity of the series' population. Review of the operative circumstances preceding each of the anastomotic failures leads to the conclusion that the method of anastomosis, as long as it is done well, is not nearly as important as the conditions under which it is done, and accordingly, the anastomotic mortality rate in distal colonic resections is primarily dependent upon the surgeon's acceptance of a proximal colostomy when fistulization, appreciable partial obstruction or active infection is present at the time of surgery.

The occurrence of anastomotic obstruction in but two cases, symptomatic stenosis in none, and symptomatic anastomotic leaks in only two cases without pre-existing complications tends to affirm our confidence in this technic of anastomosis, the principal advantage of which is simplicity.

DISCUSSION

ROBERT A. SCARBOROUGH (San Francisco, Calif.): I wish to congratulate Dr. Gambee and his co-workers for subscribing to the conviction that those who describe innovations in surgery are obligated to make known their eventual results.

Their reported experience with a single layer technic of intestinal anastomosis demonstrates mortality and morbidity figures which compare favorably with general experience of complications prior to the antibiotic era. However, our present ability to control infection has also resulted in a marked reduction in mortality and morbidity figures when more conventional methods of two-layer anastomosis are employed.

My experience in the past ten years with the use of a two-layer technic of anastomosis has resulted in a mortality and morbidity rate from anastomotic complications of about one-third those reported: mortality 1 per cent, mobidity, 3 per cent.

In self criticism, the authors have suggested that in some instances fault lay in errors of surgical judgment when proximal diversionary colostomy was not employed in instances of obstruction and infection. I doubt very much that in this series such possible errors of judgment have been made any more frequently than by myself or others in the performance of colonic resection. I do believe that in these cases a two-layer technic of anastomosis would have given an increased factor of safety.

In the final analysis, the over-all success of intestinal anastomosis will always depend upon the skill of the operating surgeon and the correct utilization of the particular technic of anastomosis employed.

WM. K. LIVINGSTON (Portland, Ore.): I have observed this procedure since its early days, before the original paper was presented to this Association by Dr. Gambee in 1946. The thing that impressed me at that time, when the paper was being written, was its reception by some of the very good surgeons in Portland (I might even use the word "horror"). Their reaction was that it was a dangerous type of procedure to perform and that it would be inadvisable to present it to a Society of this kind. On the other hand, as you will remember, it had a surprising degree of support from the members. We were very confident of the results of this procedure, as well as its simplicity. I think this latter factor impresses you first: the ability to enter the pelvis and make these anastomoses. This first paper was being written, you must understand, at a time when there were all sorts of new gadgets and clamps being invented for the so-called aseptic anastomoses; three and even more layers were utilized, which added to the possibility of obstruction and tissue strangulation in these multiple layers.

I was so impressed with this method, as well as with Dr. Gambee, that he was given the colon assignment on the medical school surgical service. This is a serious responsibility which one must be sure will not prove to be a mistake. Despite every confidence in the individual one may wonder whether this is a procedure which will do well in one man's hands but may be a mistake to teach to residents.

Over the years, with Dr. Gambee's carrying on of this assignment (supplemented by his associate, Dr. Clifford Hardwick), the procedure has more than proved itself. It has also proved to be a very valuable and safe procedure in the hands of residents, which I think is a very good test for any technic. In fact, Dr. Garnjobst was trained on this surgical service under Dr. Gambee and learned his technic under Drs. Gambee and Hardwick.

Another factor one wonders about, and which makes this type of paper so valuable, is whether the first report of a procedure may not be misleading, because sometimes a procedure looks good for a time before sufficient statistical data are obtained to be highly significant. However, this procedure has proved itself not only in the hands of experts like Dr. Gambee but also in the hands of residents on a surgical service.

JOHN A. GIUS (Iowa City, Iowa): I, too, would like to attest to the excellent presentation and the pioneering in this aspect of the craft of surgery. This is a real contribution which has been evaluated during the past ten years. Early in this period I was associated with Dr. Gambee and learned from him some of the very important aspects of anastomosis of various viscera, of which perhaps the most difficult is that of the colon.

Since that time I have had the opportunity to perform this operation many times and have also had occasion to instruct others in the use of this technic. It has been widely accepted and is utilized throughout a considerable portion of this country.

I think that the following factors contribute to the worthwhileness of this technic: it can be carried out with simplicity; no special instruments are required; no crushed tissue is placed in the anastomotic line; a minimum amount of tissue is inverted into the lumen of the bowel and, therefore, there is slight, if any, interference with the passage of bowel content.

I would also like to point out that the emphasis in the original presentation, I believe, was on the fact that the technic was a one-layer anastomosis. I would like to ask Dr. Gambee if that still prevails. It is my personal belief that while this is a real asset, if a satisfactory single layer anastomosis cannot be established, I do not hesitate to add several sutures at points where I believe that one layer may not be sufficient to maintain the union.

The second point that I would like to mention is the use of the occlusive sutures placed around the bowel to prevent the passage of contaminating material into the operative field. I have extended this by placing a second occlusive suture proximal and distal to the tumor and dividing the bowel between the sutures. Thus, the possibility of implantation of exfoliated cancer cells into the line of the anastomosis may thereby be minimized, according to the reports of Dr. Warren Cole.

LOUIS P. GAMBEE (closing): I wish to make one slight addition. We strive to complete the anastomosis with but one layer of interrupted sutures but never hesitate to use additional ones if such is indicated. Each suture must serve a definite purpose or it should not be placed.

Electrolyte Studies in Experimental Animals during Hypothermia

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THE use of hypothermia in cardiac surgery is increasing in this country and abroad. Much experimental and clinical work has been done to find a means of making this useful tool safe and to expand its practical applications. At the present time body cooling is used primarily to decrease oxygen requirements in patients with cyanotic heart disease and to permit short periods of cardiac inflow stasis for certain intracardiac procedures. The direct vision repair of interauricular septal defects is foremost among the latter. The use of hypothermia for the repair of defects in and between the ventricles generally has not been possible because of two unexplained complications of deep hypothermia, namely, ventricular irritability during cardiac manipulation and the subsequent development of irreversible ventricular fibrillation. A second and serious drawback to the routine use of hypothermia for the repair of more complicated defects is the relatively short period of circulatory arrest permitted by the presently accepted safe temperature levels. It is believed by most workers that ten to fifteen minutes of circulatory stasis is the upper limit of safety provided by a reduction of the body temperature to between 20° and 25°C. Cerebral damage and/or uniformly fatal ventricular fibrillation follow attempts to extend this time limit at these temperatures in most instances. Our early experimental efforts were undertaken for two reasons: (1) the desire to obtain lower temperature levels that might permit more prolonged periods of circulatory interruption; and (2) the need for combating the usually fatal ventricular fibrillation which occurs at these low levels.

METHOD OF STUDY

Forty mongrel dogs ranging in weight from 8 to 20 kg. were used for the experiments which, in general, were divided into two main groups:

Group I. The animals in this group were subjected to a variety of experimental observations to see what if any alterations occurred during the cooling and rewarming process. Each animal was anesthetized with intravenous nembutal,® intubated and placed on positive pressure oxygen inhalation or allowed to breath room air. The body was completely shaved, needle electrodes for electrocardiographic recording were inserted, and a femoral artery and vein were cannulated. A Statham strain gauge was used to determine the arterial and venous pressure together with simultaneous electrocardiographic tracings. A thermistor was inserted 6 cm. into the rectum for temperature determinations. Baseline values for the following were then obtained: *General data:* temperature, heart rate, arterial and venous pressure, hematocrit, arterial and venous oxygen saturations, arterial and venous CO_2 saturations and blood pH. *Serum:* sodium potassium, calcium, magnesium, phosphates, chlorides, urea nitrogen and glucose. *Blood constituents:* Red blood, white blood and differential white cell counts, and platelets and clotting time.

The blood withdrawn for sampling was replaced by freshly drawn donor blood. Plastic bags containing crushed ice were placed around the animal, and the body temperature was lowered to 22° to 25°C. The foregoing determinations were made at 2° to 4°C. temperature

changes during the cooling and rewarming process. Warming was accomplished by the continuous application of hot, wet towels. Animals surviving the experiment were observed for several days to several weeks.

Group II. Animals in this group were prepared in a similar fashion except that each underwent controlled positive pressure respiration with either 100 per cent O_2, or 93 percent O_2 and 7 per cent CO_2. A femoral artery and vein were cannulated and thoracotomy was performed through the fourth intercostal space. The pericardium was opened and a silk purse-string suture placed about the base of the right auricular appendage. The tip of the appendage was amputated and the left index finger introduced into the right auricular chamber. The coronary sinus was located by palpation, and a short No. 8 intravenous catheter introduced into the coronary sinus through a separate stab wound in the anterolateral wall of the auricle. This catheter was carefully anchored in place with a purse-string suture, and its position was constantly checked throughout the procedure by external palpation of the coronary vein. Simultaneous blood samples were drawn from the femoral artery, and femoral and coronary veins for the following determinations: blood pH, oxygen saturation, serum potassium and calcium. The animals were then cooled until ventricular fibrillation supervened. Blood samples were drawn every 2° to 3°C. or sooner if significant changes occurred in the electrocardiogram. Dilute heparin, 10 mg. in 100 cc. of saline, was injected in small amounts into the coronary vein catheter to assure its patency.

RESULTS

Group I. The seven dogs utilized in this series were cooled to between 14° to 25°C. The same determinations were made during a long period of anesthesia without cooling on two additional control animals. The pertinent data are recorded in Table 1. The values given represent the average of the determinations made for all animals.

The arterial pressure, heart rate and arteriovenous oxygen differences decreased during the cooling process and were promptly restored to control levels on rewarming. The conduction pattern, as demonstrated by electrocardiographic tracing, showed fairly consistent changes as body temperatures were lowered. The Q-T interval became prolonged; and as lower temperature levels (25°C.) were reached, the T waves became inverted and demonstrated a pattern not unlike that seen in myocardial anoxia. Prior to the onset of ventricular fibrillation, a nodal rhythm with deep inverted T waves usually developed. All of these changes were reversed when the animals' temperatures were restored to normal levels. The electrocardiographic changes were so consistent that one could predict the imminence of fibrillation by following the electrical pattern (Fig. 1.).

TABLE 1
SUMMARY OF PERTINENT PHYSIOLOGIC CHANGES IN GROUP I ANIMALS

	Normothermic	Hypothermic	Per cent Change
Mean arterial pressure (mm./Hg)	128	71	−44
Heart rate	171	51	−70
A-V O_2 differences (%)	25.5	22	−10
Serum K^+ (mEq./L.)	3.50	5.2	+48
Serum Ca^{++} (mEq./L.)	7.1	9.7	+22
Glucose, (mg. %)	94	130	+38
Platelet count (thousands)	201	19	−95
Red blood count (millions)	5.4	6.0	+11
White blood count (thousands)	7.5	2.1	−72

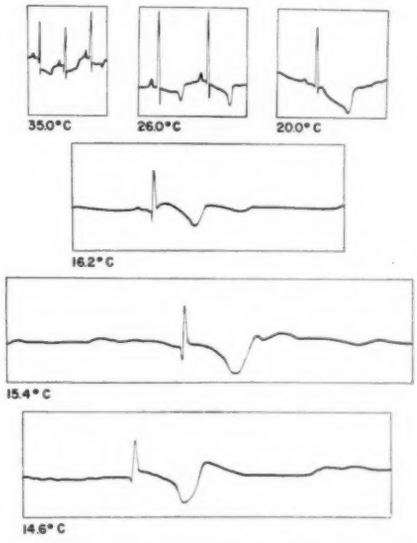

FIG. 1. Typical electrocardiographic changes during body cooling to 14.5°C.

Certain changes in the blood constituents were noted, a typical pattern of which is shown in Figure 2. The white cell count decreased in every instance, never being found higher than 2,500. Associated with this decrease in white count was a significant uniform increase in eosinophils. Platelet counts were seen to de-

crease alarmingly. One animal demonstrated a platelet count of 4,052 at 23°C. This thrombocytopenia did not disappear immediately upon rewarming, usually requiring several hours before control levels were re-established. Most of the animals showed an increase in their

TEMPERATURE	RBC	WBC	PLATELETS
35°	5.3M	6,900	123,000
33°	5.6M	2,800	90,010
28°	6.6M	3,200	8,793
26°	6.6	1,950	4,766
24°	6.1	2,200	4,052
23°	5.6	1,450	4,278

FIG. 2. Blood constituent changes during cooling and rewarming in a dog.

clotting times, one being measured in excess of eighty minutes. It has been noted by others that during thoracotomy under hypothermia there is usually a tendency for animals to ooze considerably from cut surfaces during the operative procedure. It is not unlikely that the thrombocytopenia is the explanation for this bleeding tendency.

Most of the serum electrolytes studied during this experiment showed very little alteration during cooling. Chlorides, phosphates and calcium showed an inconstant, slight increase at a temperature level of 25°C. The serum sodium was significantly increased on only one occasion. The serum potassium, however, was increased in every instance (average: 45 per cent above control levels) but promptly returned to normal levels when the animal was warmed. These alterations did not seem to be affected by a reciprocal relationship to blood pH, since in five of seven instances the animals were noted to be acidotic (pH 7.0 to 7.2) as soon as respiration became impaired by the cooling process. In these same animals potassium levels were normal at the conclusion of the rewarming period, while the pH was still depressed.

Based on these findings, six animals were cooled and hyperventilated so that blood pH was normal or increased. At a temperature of 24° to 25°C. they were subjected to inflow occlusion and right ventricular cardiotomy. Ventricular fibrillation developed in all of the animals and they died in spite of repeated attempts at electrical defibrillation and intracoronary administration of potassium as recommended by Swan et al.[5]

Group II. This experiment was designed to study the relationship of potassium and calcium in the coronary circulation during cooling to temperature levels that would produce ventricular fibrillation. Since the extracellular potassium and acid-base balance are in some way related,[5] three animals were made alkalotic by hyperventilation with 100 per cent oxygen, three were made acidotic by hyperventilation with 93 per cent oxygen and 7 per cent carbon dioxide, and three were ventilated alternately with 100 per cent oxygen and 93 per cent oxygen–7 per cent dioxide mixtures for brief periods during the cooling process.

The alterations in the serum potassium and blood pH are depicted in Figures 2 to 5, which are graphic illustrations of the typical chemical changes that occurred in a dog from each of the three categories described heretofore. It will be noted that prolonged periods of slight alkalosis or acidosis did not in any way alter the increase in serum potassium that was seen in the lower temperature ranges. This increase was as high as 80 per cent above control values in the coronary veins just prior to ventricular fibrillation in two instances. It was not related definitely to any given temperature level. A deep, inverted, rounded T wave and absence of P waves in the electrocardiogram was a fairly constant finding associated with increase in serum potassium. Premature ventricular contractions occurred at the slightest manipulation of the ventricles during this phase.

Differences in potassium concentration between artery and vein were not constant, but in six of nine dogs coronary artery potassium was from 20 to 30 per cent lower than coronary vein potassium just prior to the onset of fibrillation. The possible implication of this difference is discussed hereafter.

By varying the pH of the blood during cooling it was anticipated that a reciprocal relationship between potassium and the pH would be demonstrated as was shown in the studies reported by Swan et al.[5] Quite to the contrary, as can be seen in Figure 4, potassium levels fell with the pH depression produced by brief periods of carbon dioxide inhalation and were increased when the animals were made alkalotic by hyperventilation with 100 per cent oxygen. The over-all trend of the potassium level was one of significant increase above control values as lower temperature levels were reached, which

fact was particularly true of samples taken just prior to the onset of fibrillation. It is assumed that the marked changes in pH for brief periods was responsible for the change in potassium concentrations not found in the previous group.

Serum calcium in the coronary vein was depressed from 10 to 40 per cent of control values during cooling in seven of nine dogs. No significant difference between the serum calcium levels in the coronary artery and vein could be determined. This decrease was not unexpected in view of the potassium elevations.

Coronary arteriovenous oxygen differences remained constant down to the lowest temperature ranges reached. Peripheral oxygen differences showed a definite tendency to decrease. This has been pointed out previously by Penrod[2] and indicates the ability of the myocardium to extract oxygen from arterial blood at low temperature levels.

During this phase of experiment it was observed that at low temperature (14° to 20°C.) the coronary venous return was grossly decreased, as indicated by the greater amount of time required to collect blood samples for the electrolyte and oxygen determinations. It was believed that this represented a qualitative decrease in coronary flow. On three occasions an encircling suture was placed about the great coronary vein and the enclosed catheter, so that periodic tightening of this suture would force all coronary venous return through the catheter and allow direct measurement of that flow. Even assuming that a certain amount of the coronary drainage might pass through the thebesian system, it was thought that a crude indication of coronary flow might thus be obtained. At normothermic levels this flow was measured at an average of 90 cc. per minute, while at temperatures of 20°C. this flow averaged 21 cc. per minute. This by no means quantitatively depicts coronary flow, but one might assume a qualitative decrease on the basis of these findings.

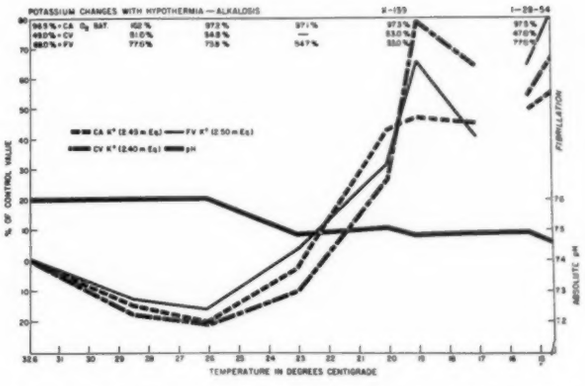

FIG. 3. Serum potassium changes during body cooling with constant elevated blood pH.

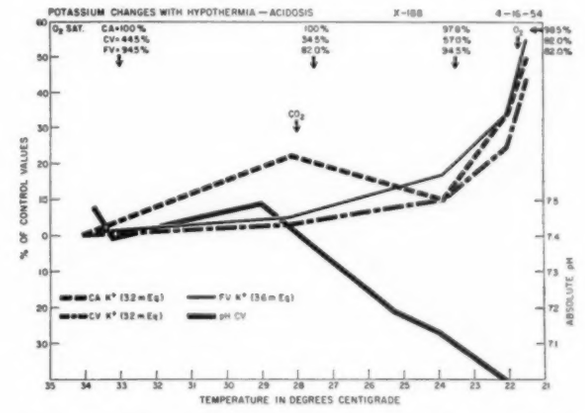

FIG. 4. Serum potassium changes during body cooling with induced acidosis.

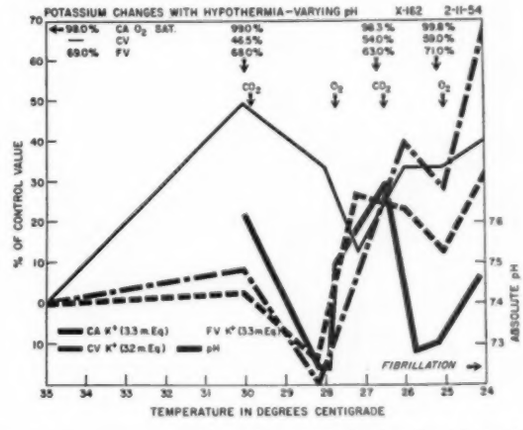

FIG. 5. Serum potassium changes during body cooling with induced blood pH changes.

COMMENTS

The interesting changes in the various determinations recorded in these experiments add to our understanding of certain physiologic and chemical alterations during hypothermia. The final explanation of myocardial irritability and the production of fatal ventricular fibrillation during profound cooling is still being sought. Rosenhain and Penrod[3] believed that because of the increased arterial and venous oxygen content and the constant or increased arteriovenous oxygen differences at low temperatures hypoxia was not a contributory factor to fibrillation. Several observations in

the present experiments suggest the existence of relative hypoxia at low temperature levels in spite of adequate arterial oxygen concentrations and the demonstrated ability of the myocardium to extract oxygen at extremely low body temperatures. These factors are: (1) an electrocardiographic pattern not unlike that seen in myocardial ischemia; (2) a reduced coronary flow as demonstrated by decreased coronary return in these experiments and by rotameter measurements reported recently by Sabiston et al.;[4] (3) elevated serum potassium, suggesting a cellular loss of potassium which is recognized as a phenomenon of tissue anoxia (a further point in support of this hypothesis is the fact that most of the group II animals demonstrated increased amounts of potassium in the venous blood just prior to ventricular fibrillation); (4) not mentioned previously but demonstrated on several occasions during this study was the fact that the electrocardiographic changes associated with deep hypothermia could be reversed temporarily by the perfusion of oxygenated blood into the coronary arteries.

Recently an open cardiotomy on an infant in intractable failure was performed for the repair of an interauricular septal defect. During the period of inflow occlusion the heart rate was approximately 6 beats per minute and the temperature was 24°C. Following release of the occluding tapes, cardiac massage was instituted but ventricular fibrillation supervened. Arterial and coronary venous blood samples were drawn and potassium levels were found to be 5.2 and 6.8 mEq. per L., respectively. No pre-occlusion controls were available in this particular case. We suggest that this elevation and arteriovenous difference might well represent tissue anoxia. Unfortunately, oxygen saturations and pH determinations were not obtained because of the urgency of resuscitative attempts.

Recently Gollan et al.[1] have reduced the body temperature of dogs to approximately 4°C. and successfully carried them through thirty-to forty-five minutes of circulatory arrest by means of a low flow pump oxygenator to augment coronary flow during the critical 20° to 14°C. level. Application of hypothermia and augmented coronary flow in this manner may prove to be a most useful means for the performance of prolonged intracardiac surgery without the use of the present day uncertain and complicated pump oxygenators.

SUMMARY

Data on physiologic alteration in dogs undergoing general body cooling and rewarming are presented.

Heart rate, mean arterial pressures, platelets and white cell counts all showed significant decreases at low temperature levels (22° to 25°C.).

Serum potassium concentrations were found to be greatly increased just prior to ventricular fibrillation in the cold state. Prolonged acidosis or alkalosis did not alter this elevation.

Electrocardiographic patterns were fairly constant with deep cooling and could be used to predict impending difficulty.

It is suggested that a relative tissue hypoxia associated with low coronary flow is a factor in the production of ventricular fibrillation during profound hypothermia.

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DISCUSSION

Rodney T. Smith (closing): Recently an open cardiotomy for repair of interventricular failure was performed on a child in an attempt to close the defect. Shortly after the release of the tapes irreversible ventricular fibrillation developed. During the process we had an opportunity to extract some arterial blood; also, a small needle was placed in the coronary vein and venous samples were extracted. At this time, potassium values of those particular samples were about 5 and 6.4, respectively, which I think was a significant elevation above the normal values.

Some Aspects of Hospital Infection

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The problem of hospital infection is not new and the history of the efforts to control it forms an interesting study in itself. For a time following the introduction of penicillin and the apparent control of the streptococci and staphylococci, it appeared that such difficulties as had persisted would be eliminated. We are indeed fortunate that the streptococcus has remained vulnerable to the antibiotics, but the gradual emancipation of the staphylococcus has brought us back to our previous position insofar as infections with that organism are concerned. We think it fair to say that now we have only slightly more effective means of dealing with the majority of staphylococcal infections arising in a hospital than we had in the pre-antibiotic era.

Thus, our attention must be redirected to the question of prevention of cross infection which involves, initially, a study of the reservoirs of infection in a hospital.

We would feel easier in describing, as we propose to do, our difficulties, and in revealing the extent of contamination of the hospitals with which we are associated if we knew that all other institutions were similarly affected.

Perhaps there will be some physicians whose experience parallels ours. There may be others whose hospitals are contaminated but who are as yet unaware of the fact, and there will be still another group whose hospitals are uninfected. To this last group we can only express our admiration if, indeed, the purity is the result of a faultless technic. If, on the other hand, they have by chance remained free of contamination and if they have not developed a counterinfection technic superior to that which prevails generally on this continent, we would warn them that their days of freedom may be limited; we have already seen pride shattered in several of our own hospitals.

During the past six years we have seen a wide variety of infections involving all types of patients, both young and old.

By far the most common site to be involved is the skin, and boils are the result. They appear on any part of the body surface, most frequently on the backs of patients confined to bed, and can be most distressing and persistent. We are, at present, trying to determine the best treatment for boils and, more important, to discover a means of preventing their repeated recurrence—a strange pursuit in this enlightened age of surgery, but one which promises to be of unexpected interest.

Wound infection is the next most common form that we see. Occasionally it develops early in the form of an acute massive infection, but more frequently appears relatively late in the postoperative course (eighth to ninth day) and produces a slow, grumbling, indolent type of reaction. Wound infections, like boils, have frequently made themselves apparent only after the patient's discharge from the hospital, a feature which makes the gathering of statistics difficult.

Staphylococcal pneumonia is more frequent now than before. Some patients are admitted with the disease; in others it develops in the hospital. That terminal staphylococcal pneumonia should develop in patients dying of some incurable disease is of no particular concern. However, it is alarming to see staphylococcal pneumonia develop as a complication (in some instances, lethal) in other patients whose primary disease is not ordinarily fatal. Staphylococcal enterocolitis, parotitis and septicemia have all occurred.

Thus, it is quite apparent that in our hospitals infection is common. We would like to

FIG. 1. Dressing covering a small quantity of fluorescent powder scattered on the intact skin.

FIG. 2. Twenty-four hours after application of the dressing. Ultraviolet light reveals the powder to have passed through the dressing and to have covered the sheet (turned back) and the mattress.

be able to express our position in accurate terms, but having been involved in this particular problem for some time and having personal knowledge of the difficulties in amassing accurate data unless they are collected in the process of a specific and limited project, we are profoundly suspicious of figures that are presented to indicate the frequency of infection in hospital cases. Therefore, for the purposes of this presentation we prefer simply to state that our problem is very real. We sometimes wish that it were more dramatic, for if it were, it would be easier to get the full cooperation of doctors and others which is so necessary for its elimination.

No one doctor sees many cases in his own practice. He is incensed when one of his patients becomes infected, but soon lapses into a condition of apathy and remains there until the next personal episode. Only a panoramic view of the work in a hospital will give a true impression of the situation.

How is it that this organism (which is so easily killed by a moderate degree of heat and by many antiseptics) can create such havoc in a hospital that is, to all outward appearances, spotlessly clean? The well known answers are these: (1) the staphylococcus can survive and maintain its virulence for a long time in dry fine dust; and (2) fine dust has extraordinary powers of movement and penetration.

To illustrate the first point, one of us (J. C. C.) was successful in culturing staphylococci from the surface of mattresses that had been stored undisturbed in a dry storeroom in one of our hospitals for many months.[1]

The second point can be usefully demonstrated by experiments using fluorescent powder. These experiments will be described in greater detail elsewhere. In one test, a small quantity of this powder is sprinkled on the skin of a patient's leg and a bulky dressing is carefully applied and held in place with adhesive strips. (Fig. 1.) The patient is allowed to move about at will in bed. If the room is examined with a Wood's lamp twenty-four hours later, it will be found that the fluorescent powder has scattered widely and has even passed through the sheets onto the surface of the mattress. (Fig. 2.)

In another experiment, a small gauze bag (Fig. 3) containing fluorescent powder is hung from the waistline of a surgeon's undershirt. Operating trousers and gown are then put on

FIG. 3. A gauze bag filled with fluorescent powder is pinned to the vest of the surgeon.

FIG. 4. Ultraviolet light shone on one of the drapes reveals spots of fluorescent powder that have passed through the surgeon's gown during the course of the operation.

in the usual fashion and with the usual care. At the conclusion of the operation, examination of the sponges and side towels under ultraviolet light will reveal scattered patches of fluorescent powder. (Fig. 4.)

The spread of organisms about a hospital room has been demonstrated in the following experiment. A room with its adjoining bathroom was completely "cleaned up." Beds, floors, walls, chairs, tables, bath, toilet seat, wash basin, door handles and the like were all carefully swabbed down with an antiseptic solution. Freshly autoclaved mattresses, freshly laundered sheets, blankets, pillows and pajamas were supplied. Preliminary culture of all these objects revealed that all were free of staphylococci, with the exception of a single colony recovered from the lavatory seat. Two patients with "open staphylococcal lesions" were then placed in the room to live and move about at will. It was shown that within a short space of time all the aforementioned objects were grossly contaminated with staphylococci. (Table 1.) Building upon evidence of this type, it is not difficult to map out the spread of contamination in a hospital. (Fig. 5.) The infected patient will contaminate all that he touches and much that is well beyond his reach.

What can be done to reduce the hazard to the patient? Theoretically, it should be possible to eliminate it. Practically, the solution is not easy to find. We have not even come close, as yet, to reducing the incidence of infection in our hospitals to an acceptable level (whatever that may be). We have, however, learned certain things which might be worth reviewing.

In certain circumstances, at least, and for a time, infection can be brought under control. Drs. Hardyment, Wilson and Cockroft at the Vancouver General Hospital have, for the past six years, been studying the problem of staphylococcal infection in the Newborn Nurseries. A preliminary report of their work has been made[2] and a further report is to be published

TABLE 1

Source	Results of Cultures		
	Preliminary	First Day	Second Day
Mattress	−	−	+
Bed table	−	+	+
Bath	−	+	+
Wash basin	−	+	+
Lavatory seat	+	+	+
Blanket	−	−	+

soon. During this time they have gradually developed a technic which, during the past eight months, has resulted in the virtual elimination of pyoderma in the infants passing through these nurseries. To us, the discouraging fact is that it took this capable team so many years to achieve success. The newborn are admitted to the ward sterile; they do not come in with boils and hand infections as adults frequently do. To sterilize the mattresses, blank-

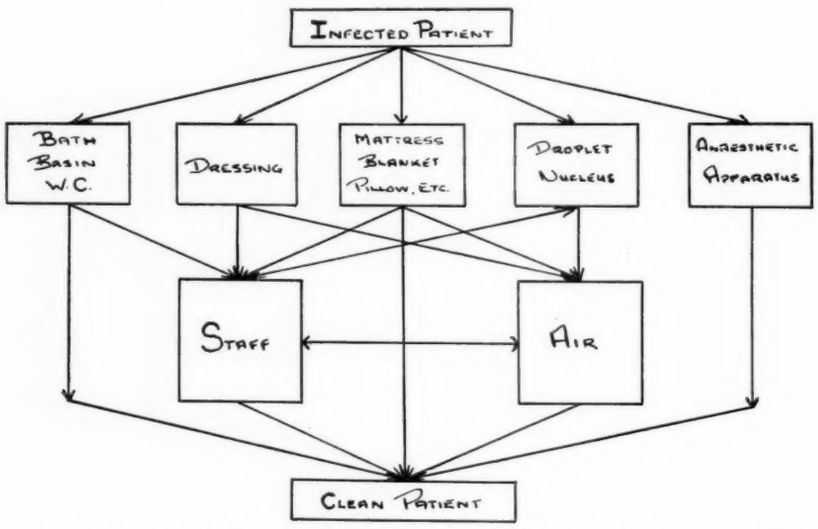

Fig. 5. Some of the routes of infection passing from patient to patient.

ets, sheets, towels and clothing—in fact practically everything with which the infant might come in contact—is a relatively simple matter (relative, that is, to achieving the same for the adult patient). These infants are not regularly transported about the hospital to operating room and x-ray, they receive few, if any, visitors and their stay in the hospital is usually short. All these factors tend to reduce the likelihood of infection. Finally, nurses and doctors are more likely to cooperate fully in the carrying out of technics when dealing with children than when treating adults. Were it not for the fact that infants are said to be, and probably are, much more sensitive to staphylococcal infection than adults, one would be inclined to despair of ever achieving success in adult wards.

We have learned that the problem is anything but a simple one; it extends into nearly every activity of a hospital.

To correct the situation in a contaminated hospital, it is necessary to attack the responsible organism constantly and on all fronts. To leave one small reservoir uncontrolled may permit widespread contamination. The magnitude of the task will be appreciated only by those who have attempted it, and may be illustrated by a brief description of some of the new measures we have adopted in one of our hospitals.

MEASURES USED TO COMBAT INFECTION

Isolation Ward. In this hospital we have established an isolation ward to which all patients known to have infection are admitted and to which those patients in whom infection develops while on other wards of the hospital are transferred. For those patients who cannot possibly be transferred, because of the particular circumstances of their illness, a type of barrier nursing is carried out in the ward, preferably in a side room. It need hardly be said that this barrier technic, even though most conscientiously followed, is not fully efficient and inevitably contamination will spread from the surroundings of the infected patient to the remainder of the ward. However, we believe that incomplete as the protection is, barrier nursing is worth while.

Care of Blankets, Mattresses and the Like. Random cultures taken from these objects have shown a high percentage of positive results. This fact has led us to the conclusion that they are a most important reservoir of infection. It is no exaggeration to say that a patient being put to bed in a contaminated hospital has a very fair chance of being literally surrounded by staphylococci. It has been shown that the sheets which are virtually sterile following laundering provide no useful barrier to the migration of organisms. Thus, the patient may be attacked by staphylococci in the rear from the mattress and in front from the blankets, while the nape of the neck and the back of the head are constantly being showered with organisms from the infected pillow. The treatment of all of these articles is difficult. Mattresses can be autoclaved, and many hospitals have an autoclave of sufficient size to handle

them. However, in an experiment it was discovered that to autoclave an ordinary spring-filled mattress ten times would ruin it. Therefore, we have adopted the device of treating the mattresses with formalin vapor in an autoclave. So far as our studies are concerned, this would appear to be a satisfactory technic. However, there is a distinct limit to the number of mattresses that can be autoclaved in a day and we are conducting intensive research into the question of mattress covers. We are particularly interested at the present time in using a ticking mattress cover which can be easily applied and which, when treated with oil and an antiseptic, seems to limit the spread of organisms through to the mattress. Pillows and blankets have been laundered by an ordinary laundering process, but we are not yet satisfied that this process is adequate. Recently, we were discouraged to find some of our blankets coming back, still infected, from the laundry. Our present technic is to treat the mattresses of all infected patients with formalin vapor at the time of the patient's discharge from the hospital or transfer from the ward, and to supply each new patient with a freshly laundered set of blankets, pillows, sheets and pillowcases.

Handling of Dirty Linen. Our laundry processes have all been reviewed and appear, in most instances, to be adequate. We did find, however, that our dirty laundry was being taken from the wards in the same trucks that delivered the clean laundry to the ward. In other words, there was a real chance of the clean laundry being contaminated in the final stage of transport. This has been, we hope, corrected by supplying canvas cases which can be sterilized for the laundry trucks.

Housekeeping. In order to try to keep down the amount of dust in the air, we have, for the present time, abandoned dry dusting, dry sweeping and floor polishing in the ward areas. We have no real evidence to suggest that this will help the situation, but can state that the floors do not look as ill-kept as we thought they might. Bath tubs and basins are regularly decontaminated with antiseptics.

Washing Facilities. It is unusual for a hospital to have enough suitable washing facilities for the nursing and medical staff, and the design of many modern wards omits this important item. We have, where possible in this hospital, installed in strategic places wash basins with elbow taps and mixing faucets. Cake soap has been found infected in a number of instances so we have abandoned it and have adopted liquid soap entirely for both staff and patients.

Theatre Technic. We have gone carefully through all our surgical technics and have found it necessary to make only the following changes: We thought that our technic of preparation of the skin of the patients for operation was not as careful as it might be, and we have introduced a system whereby the patient is prepared in the operating room the night prior to operation by orderlies who are scrubbed, gowned and gloved, and wear masks. They work with sterile razors and new blades, and apply an antiseptic to the patient's skin following the shave. We have no evidence to suggest that this will help, but, theoretically, it appears to us to be a sound procedure.

We have been investigating the use of some occlusive and some antiseptic dressings and believe that we have much to learn from the writings of Lord Lister seventy-five years ago. To prevent contamination of wounds covered by dressings soaked with discharge, he used various forms of antiseptic dressings; we are investigating these at the present time. Likewise, we believe that the ordinary gauze dressing is not occlusive, and we are investigating various types of plastic materials which we think might be more efficient.

Following the experiments showing the spread of dust through operating gowns, we feel bound to wear sterile plastic aprons in this hospital.

It was not surprising to us to find that there was a certain amount of contamination of the McGill tubes and the rubber connecting hoses of the anaesthetic machines. An effort is now made to decontaminate these by boiling the McGill tubes and by soaking the connecting hoses in an antiseptic solution (CTAB).

CONCLUSION

We have outlined some of the problems caused by staphylococcal infection in a hospital, and have described what we believe to be the important reservoirs of this infection. We have discussed briefly some of the new measures that we have taken in an effort to eliminate these reservoirs. We do not wish to convey the impression that we have by any means conquered the problem. We feel very

strongly that it should be appreciated that the problem is an extraordinarily complex one, but that even though it may never be possible to eliminate every source of infection, we think it likely that worth while results can be obtained by an energetic program.

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DISCUSSION

Wm. B. Hutchinson (Seattle, Wash.): This paper has been most interesting and instructive. Dr. Robertson must certainly be congratulated for the thorough manner in which he has directed his hospital in their search for the answers to staphylococcal infections. All of us have been slow to recognize the seriousness and the far-reaching implications of the problem. The individual who enters a hospital for a single elective procedure and contracts an antibiotic-resistant staphylococcal infection necessitating a six- or eight-week loss of work has a problem deserving real study. If the surgeon sincerely seeks correction of the hospital infection dilemma, the rest of the staff usually fall in line.

When the various antibiotics were first introduced they were roughly 95 per cent effective against all strains of staphylococcal organisms. Today three-fourths of the strains are resistant to all the antibiotics except chloromycetin® and erythromycin whose effectiveness will no doubt meet the same fate in the near future.

We have observed that a delayed infection will more often than not develop in patients receiving antibiotics. This is exemplified in the wound infection which is manifest ordinarily in three to eight days, but now with the antibiotics may take even two or three months to be recognizable. The patient may not run a septic course as would be anticipated. Our own incidence of wound infections has risen sharply in the past two years. We have stopped using antibiotics for the routine intra-abdominal operation involving the stomach or bowel. Our incidence of wound infection seems to have been reduced.

Breast abscesses have been a major problem in our practice. In the past year we have drained more breast abscesses in postpartum mothers than we did in the previous fourteen years. This was the result of an epidemic of staphylococcus infections at the Swedish Hospital which occurred on our obstetric service. In a five-month period at the Fort Lawton Hospital, Seattle, twenty-four mothers and nineteen babies had breast abscesses. The infants acquired the staphylococcus from the nursery personnel. The incidence of breast abscesses in the mothers dropped precipitiously with the cessation of nursing.

The authors mentioned the importance of the nose and throat carrier, but I should like to emphasize this. The noses and throats of hospital personnel which are teeming with antibiotic-resistant staphylococcus will cause infections with alarming frequency regardless of the condition of the laundry, mattresses and the like. This represents to me the most frequent source of contamination and certainly the most difficult one to detect and to treat. Over a three-month period at the Marine Hospital in Seattle in 1954 postoperative staphylococcal pneumonia developed in twenty-five patients, resulting in three deaths. This infection was traced to one nurse carrier in the recovery room, and was controlled by transferring her. In any hospital where elderly patients are being operated upon there are probably many cases of staphylococcal pneumonia that go undetected even at postmortem examination. What must be done with these staphylococcus carriers? Must these carriers be discharged, treated or moved? It must be noted that they are not all nasopharyngeal carriers. At King County Hospital a linen room attendant was detected with a chronic osteomyelitis which had caused a series of staphylococcal operating room infections; these ceased when she was replaced.

The literature has been replete with many practical answers to the problems that this paper has presented so clearly. I should like to see our hospital set aside a very strict isolation ward for all patients with staphylococcal infections, and then treat them with the same surgical respect accorded cases of gas gangrene. This may be impossible in a private hospital.

In recent years in our locality there has been an overcrowding of patients due to lack of sufficient hospital accomodations in the area. This may be a factor in disseminating staphylococcus.

With the continued overuse of the antibiotics we have created a new world of organisms. It may just be conceivable that surgeons may again have to learn how to treat infections, a lost art in the past decade.

J. Karl Poppe (Portland, Ore.): I have been much impressed with the report of Dr. Robertson and his co-workers. It makes me think more seriously of my own experiences recently. In retrospect, I can think of an alarmingly high number of infections which have occurred in the last three months in one ward in one hospital. Eventually, after changing antibiotics several times without success against the staphylococcal in-

vaders, I was forced to change my operative technic, reverting to the more meticulous technic used ten or fifteen years ago with more drains and more intercostal thoracotomy tubes to eliminate fluid accumulations and dead spaces, as in the pre-antibiotic days.

GORDON SMITH (Los Angeles, Calif.): This paper has been most timely and has pointed out the fact that we are living in a dream world regarding infection. The authors have shown how difficult it is to prevent contamination of the surgical patient with staphylococci. There is one additional point I should like to mention. A great many people believe they can put a seromuscular suture in the bowel without contaminating the needle and the instruments which are used to place this suture. This is a fallacy.

In the early 1930's Dr. Roy Hammack, a pathologist, and my father cultured all purse-strings used for seromuscular sutures during a six-month period at the Hospital of the Good Samaritan in Los Angeles. They found that every purse-string suture was contaminated with bacteria from the bowel.

I would also like to make a plea for the omission of occlusive dressings. Almost any wound can be cultured immediately after closure of the skin and will be found to be extensively contaminated with bacteria, predominantly staphylococci. The best medium for staphylococci to increase in numbers is one which is moist and warm. When staphylococci are put in the cold with no occlusive dressing and with no moisture they will not live, and the instance of wound infections will decrease considerably.

LOUIS P. GAMBEE (Portland, Ore.): I am constrained to comment on this paper because it has a particular significance to me. I work in the newest hospital in Portland. We fared very well until early in 1955 when it became necessary to remodel part of our surgical department. Most of the reconstruction was done in the hall that led to the theaters. Within a short time we began to encounter wound infections. Some of these infections occurred in patients who had had back fusions; others in patients who had had discs removed. A series of infections in the abdominal wall was noted. In three instances I had repaired a hiatal hernia. In several patients I had performed gastric resection or had repaired an inguinal hernia. My experience was not unusual during this period. Repeated conferences led us to conclude that dust arising from the remodeling work was probably a cause of the infections, in spite of the fact that the reconstruction was being done at night and on week-ends as far as was possible.

H. ROCKE ROBERTSON (closing): Dr. Hutchinson has brought up the question concerning nasopharyngeal carriers. This is important, it is true, but one or two things have come up which make me wonder how important the nasopharyngeal carrier is. I will cite two instances briefly.

First, in our infants' ward the incidence of skin infection and all other staphylococcal infection has been next to nothing for about eight months, whereas the nasopharyngeal carrier rate among the attendants has remained the same. One would think that if the nasopharynx was an important source of infection, the infection rate in the infants would not have stayed down so low for so long.

A second example was reported in the literature not long ago. In a children's ward there was a very high carrier rate among the attendants but no infections in the ward, until one of the attending staff developed a boil; then the rate among the infants went up very high. I rather think active infection is infinitely more important than is a heavy nasopharyngeal flora in an attendant who is normally clean in his habits.

Dr. Poppe mentioned the question of changing operative technic which leads me to say that we, too, have reviewed our technic. I will not argue about the value of drains but I must say that I am more inclined to agree with Dr. Shidler in his point of view.

I agree in some ways with Dr. Smith's point about the occlusive dressings. However, when seeing such a high bacterial count in blankets, it has made me afraid to leave wounds exposed, and I have not done it. In the few instances in which we have used antiseptic dressings to see their effect, the wounds have been extraordinarily good and absolutely reactionless.

Finally, I would like to reiterate that this problem is complex. So often you find one factor—a carrier, an infected patient or an interne—which seems to account for an epidemic in a hospital, and you may think that the elimination of this one factor will solve your problem, but it will not. We have found that one single factor is never responsible, but rather many factors.

The Use of Teflon Fabric as Arterial Grafts

AN EXPERIMENTAL STUDY IN DOGS

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Two factors primarily have caused surgeons to seek materials other than homografts for use as large vessel replacements. First, homografts are not universally available because of lack of suitable arteries for preservation, or lack of suitable equipment and personnel for the preservative process. Second, the fate of homografts has been unpredictable in that they frequently manifest an acceleration of the usual degenerative processes. These consist of subintimal calcific placques, intimal cracking, hemorrhage, thrombus and aneurysm formation. These changes have been observed clinically as well as experimentally.[1,2]

It was recognized early in the evaluation of the fate of homografts that the non-viable media served only as a matrix for internal and external covering by the host vessel fibroblasts. Consideration was given early in the century toward using glass and metal tubes as permanent intravascular grafts, but these failed because of thrombosis and severance of the host vessel by ligature.[3] Hufnagel found that the highly polished non-wettable surface of methyl methacrylate tubing reduced the incidence of thrombosis found with other prosthetic tubes. These tubes could be held in place by nylon circumferential multiple point fixation clamps which prevented host vessel severance and hemorrhage.[4] Only short arterial defects, preferably of the aorta, and not of joint-bridging areas, could be grafted successfully by these rigid tubes. Experiences in the use of rigid tubes in treating battle arterial injuries pointed out these limitations.[5] In 1952 the first report on the use of the more adaptable plastic fabrics fashioned into tubes for arterial grafts by the usual suture technics was made by Voorhees on vinyon N.®[6] Shumacker[7,8] recently reported the use of fused nylon cloth and polythene film, and Hufnagel[9] the use of orlon fabric as successful pliable vascular grafts. Edwards has treated woven seamless nylon tubes with a solvent to decrease porosity and permit crimping for increased flexibility.[10]

Deterling has made a critical analysis of the important physicochemical properties of several commercially available thermoplastic fabrics.[11] A comparison of blood loss through the fabric, ease of fashioning, and suturing the tubes, as well as the early and late fate of the tubes, was made. A dacron taffeta weave with a thread count of 116 by 100, thickness of about 0.003 inch, and a porosity of 4 to 8 cubic feet of air was preferred. A nylon taffeta fabric with a thread count of 166 by 116, thickness of about 0.004 inch, and porosity of 4 to 15 cubic feet also was used successfully. The best of the available orlon fabrics studied contained a thread count of 116 by 84, thickness of 0.005 inch, and porosity of 46 cubic feet of air.

Non-permeability, chemical inertness, low porosity, pliability, ease of procurement and sterilization are desirable qualities of any plastic fabric to be used as a vascular prosthesis. Teflon* (polytetrafluoroethylene) fabric is notable because of its non-wettability, chemical inertness and strength. The fibroblastic response to implanted teflon has been shown to be minimal.[12]

The subsequent report deals with the experimental use of certain teflon fabrics.

MATERIAL

Teflon fiber is dark to light brown in color and has the following characteristics: tenacity,

* Manufactured by E. I. duPont de Nemours & Company, Arlington, New Jersey.

TABLE I

Physicochemical Properties	Nylon	Orlon	Dacron	Teflon
Specific gravity	1.1	1.2	1.4	2.3
Melting point (°F.)	480	455	480	620
Tenacity (gm./denier)	6.0–7.8	4.7–5.3	4.8–6.2	1.6–2.0
Tensile strength (lb./sq. in.)	88,000	75,000	90,000	50,000
Elongation at break (%)	15–23	15–17	12–20	15–33
Response to heat (°F.)	Sticky at 455	Sticky at 455	Sticky at 455	High resistance
Resistance to acids	Poor	Poor to H_2SO_4	Poor to H_2SO_4	Excellent
Resistance to alkalis	Good	Poor	Poor	Excellent
Solvent	Formic acid	Ethylene carbonate	Metacresol	None

1.6 to 2.0 gm./denier; elongation at break, 15 to 33 per cent; is not affected by moisture, sunlight, heat up to 400 to 500°F., nor age; and is inert to acids, alkali, organic solvents, bacteria and fungi. Commercially it is used as packing, gaskets, air or fuel filtration, conveyor belts, and because of its chemical inertness, as a chemical filter cloth. A comparison of the physicochemical properties of the various thermoplastic fibers[13] is given in Table I.

TABLE II

Fabric	Thread Count (warp and filler)	Thickness (0.001 inch)	Porosity (air, cu. ft./min.)	Fiber Size (microns)
T-3	76 × 69	9.7	9.86	165
T-8	76 × 65	9.1	3.43	130
T-10	142 × 44	16.7	1.86	145

The fiber is manufactured into various fabrics dependent upon the commercial interests of the company. Because the fiber exhibits many features considered to be ideal for vessel replacement, a number of companies utilizing teflon fiber were contacted and a sample of their product obtained together with other pertinent information. Of all teflon fabrics studied, three were considered to be of potential value. (Fig. 1.) These were identified by the manufacturer as T-3, T-8 and T-10. The characteristics of these three weaves are shown in Table II.

METHODS OF STUDY

Sixty mongrel dogs, weighing between 7 and 17 kg., were used in the study.

Operative Procedure. All animals were anesthetized with intravenous nembutal® and maintained by a positive pressure respirator administering oxygen and ether mixture through an endotracheal tube. All but two grafts were in the thoracic aorta. Left thoracotomy through the seventh intercostal space with posterior rib sections was performed routinely. Mobilization of the aorta was accomplished by sectioning the intercostal arteries. A segment of the aorta was resected. In each animal an attempt was made to insert a graft of the same length and diameter as the resected aorta. (Fig. 2.) These grafts were implanted without the aid of hypothermia. Intraluminal shunts of polished lucite were used to restore blood flow while the distal and two-thirds of the proximal anastomoses were being made. The aorta was again occluded while the shunt was removed through the in-

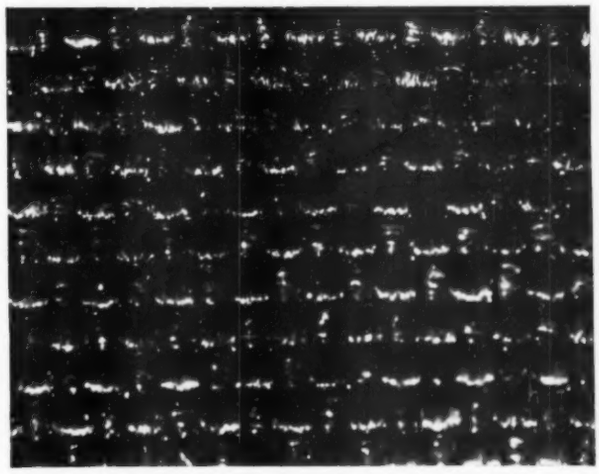

FIG. 1. Photomicrograph of fabric T-8 showing surface texture of the uncalendered taffeta weave (original magnification × 12).

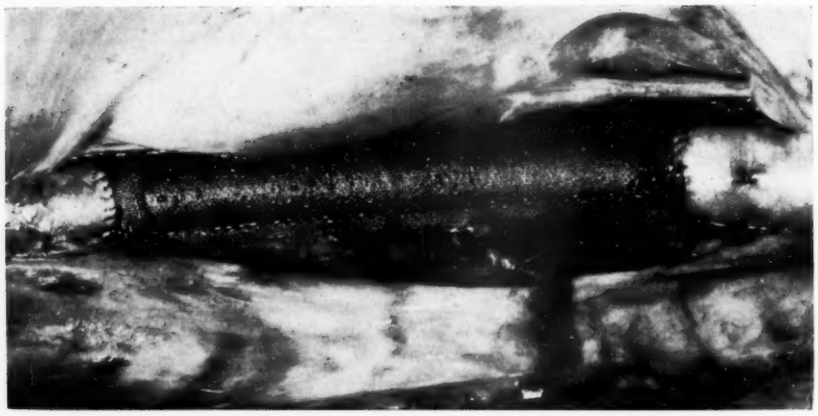

FIG. 2. An operating room example of a graft functioning within one minute after completion. There is only serous transudation through the fabric interstices.

completed proximal anastomosis. The shunts have circumferential grooves on each end onto which the aorta was tied by a heavy cotton ligature. Blood was not shunted in the abdominal aortic grafts. Coarctation clamps were used for aortic occlusion.

Anastomoses were made by a suture of No. ooooo braided silk on a fine atraumatic® needle. A continuous over and over whip stitch was used. The only special point in the suturing technic was to reinforce the junction of the graft seam with the host vessel. The grafts were covered with pleura or peritoneum. The lungs were carefully expanded and the intrapleural air removed by a temporary chest catheter. Each animal was given only one injection of long-acting penicillin preparation postoperatively. They were kept in separate cages for two weeks, and then allowed to run together in paddocks.

The Graft. The teflon grafts, which had diameters ranging from 0.6 to 1.2 cm., were previously prepared by suturing doubly on a sewing machine using a fine needle, close stitch and nylon thread. The grafts ranged in length from 2.5 to 12.0 cm. and averaged 5.2 cm. These were washed three times with septisol and warm water to remove all plasticisers or additives. The initial twenty tubes were sterilized by soaking in a 0.1 per cent solution of aqueous zephiran® for twenty-four hours; the last forty by autoclaving for twenty minutes. Ordinarily, tubes several inches in length were sterilized, and appropriate portions of these were used to bridge the resected defect of thoracic aorta.

Other Studies. The animals were examined periodically for palpable femoral arterial pulsations and were sacrificed at about monthly intervals up to three months. Additional animals were sacrificed at six and twelve months postoperatively. At autopsy approximately ten grafts in animals surviving over six months were exposed to intraluminal pressures as high as 500 mm. Hg in order to determine the "bursting strength" of the graft. Gross and microscopic examinations were made of each anastomosis and other appropriate areas.

RESULTS

The over-all results are recorded in Tables III to V. Actually, very little difference was observed in the behavior of the three different teflon fabrics. Blood loss was minimal from each fabric and the anastomoses, averaging about 75 ml. There was slight serosanguinous ooze through the interstices of the fabric for three or four minutes. The anastomotic blood loss was no greater than with vessel-to-vessel grafts. There was slightly more blood loss through the more porous T-3 fabric, but still not more than 100 ml. on the average.

Generally, the graft is immediately coated on its inner layer by a fibrinous lining. This gradually becomes thicker until at about four weeks it averages 0.7 to 1.0 mm. in thickness. Endothelium apparently grows into the graft from each end of the host vessel replacing the fibrinous coat with a smooth, shiny, translucent membrane. (Fig. 3.) The onset and rate of growth is unpredictable but usually begins at about four weeks and progresses at a rate of

TABLE III
FABRIC T-3

Dog No.	Diameter (cm.)	Length (cm.)	Postoperative Days	Thrombosis	Endothelium	Sterilization	Course
T-101..	0.8	4.5	300+	0	.....	Autoclave	Alive; femoral pulsation normal
T-102..	0.8	4.0	275	0	Total	Autoclave	Sacrificed
T-103..	0.8	4.0	91	0	20 mm.	Autoclave	Sacrificed
T-104..	1.0	4.5	84	0	12 mm.	Autoclave	Sacrificed
T-105..	1.2	4.5	265	0	Total	Autoclave	Sacrificed
T-106..	0.8	4.0	20	0	None	Autoclave	Uterine hemorrhage
T-107..	1.0	6.0	280+	0	.....	Autoclave	Alive, femoral pulsation normal
T-108..	1.0	4.0	64	0	4 mm.	Autoclave	Sacrificed
T-109..	1.2	4.5	63	0	8 mm.	Autoclave	Sacrificed
T-110..	1.2	6.0	63	0	Total	Autoclave	Sacrificed

TABLE IV
FABRIC T-8

Dog No.	Diameter (cm.)	Length (cm.)	Postoperative Days	Thrombosis	Endothelium	Sterilization	Course
T-51...	1.0	4.0	96	0	6 mm.	Zephiran	Sacrificed
T-53...	1.0	6.0	1	0	None	Zephiran	Pneumothorax
T-54...	0.8	3.0	386	0	Total	Zephiran	Sacrificed
T-55...	1.0	5.7	203	0	Total	Zephiran	Sacrificed
T-59...	1.2	6.0	365+	0	.....	Zephiran	Alive; femoral pulsation normal
T-63...	1.0	7.0	66	0	6 mm.	Zephiran	Sacrificed
T-64...	1.0	3.7	5	0	None	Zephiran	Pneumothorax
T-69...	1.0	7.0	6	0	None	Zephiran	Wound dehiscence
T-70...	1.0	11.5	1	0	None	Zephiran	Hemorrhage at proximal shunt tie
T-72...	0.8	5.5	45	0	3 mm.	Autoclave	Sacrificed
T-74...	0.6	5.5	1	+	None	Autoclave	Thrombosis at proximal shunt tie
T-77...	0.8	4.0	156	0	14 mm.	Autoclave	Sacrificed
T-78...	0.6	4.0	337	0	Total	Autoclave	Sacrificed
T-79...	0.8	4.0	154	+	4 mm.	Autoclave	Thrombosis
T-80...	0.6	3.5	335	0	Total	Autoclave	Sacrificed
T-81...	0.8	3.0	331	0	Total	Autoclave	Sacrificed
T-82...	0.6	4.0	153	0	Total	Autoclave	Sacrificed
T-83...	0.8	4.0	1	0	None	Autoclave	Hemorrhage at clamp site
T-84...	1.0	3.5	147	0	Total	Autoclave	Sacrificed
T-85...	1.0	4.0	147	0	Total	Autoclave	Sacrificed
T-86...	1.0	3.5	21	0	2 mm.	Autoclave	Sacrificed
T-88...	1.2	4.0	145	0	2 mm.	Autoclave	Sacrificed
T-89...	1.2	7.0	300+	0	.....	Autoclave	Alive; femoral pulsation normal
T-91...	1.2	7.5	300+	0	.....	Autoclave	Alive; femoral pulsation normal
T-93...	1.2	4.5	135	0	2 mm.	Autoclave	Sacrificed
T-98...	0.8	3.5	126	0	Total	Autoclave	Sacrificed
T-100..	0.8	3.5	118	0	12 mm.	Autoclave	Sacrificed

approximately 5 mm. per month from each end until after about five or six months when isolated islands of endothelium appear throughout the graft. Complete endothelialization occurs shortly. (Fig. 4.) Actually, there was so little fibrotic reaction surrounding the grafts that most of them were visible beneath the thin pleural or peritoneal covering when sacrificed. Neither the thin inner endothelial lining nor the external fibrous sheath would readily separate from the fabric because of fibroblastic growth into the interstices.

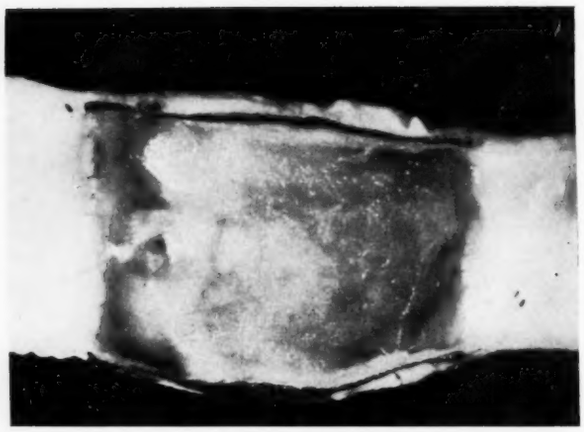

FIG. 3. Autopsy photograph of a ninety-six day old graft of fabric T-8 showing 6 mm. of endothelial growth from each end replacing the fibrinous coating.

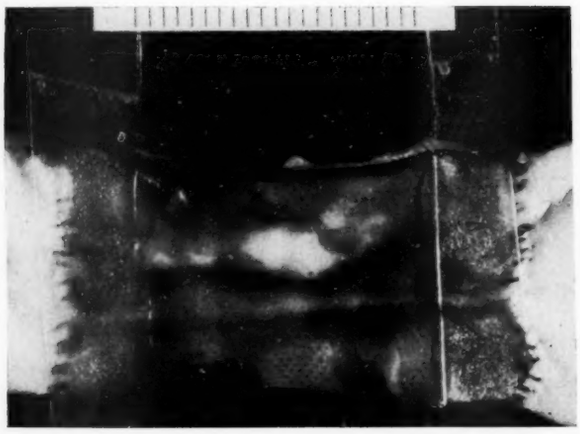

FIG. 4. After six or more months the endothelial-like membrane completely replaces the fibrinous coating and adheres tightly to the fabric. This graft of fabric T-10 is totally smooth and translucent, having been in an animal 345 days. The white area in the central portion is not calcification.

Technically, T-8 and T-10 held a crease better and showed less tendency to ravel, while T-8 and T-3 were more pliable and soft. No remarkable differences were noted in tissue response to the three fabrics. Fibrinous and endothelial growth was essentially the same in each. The amount of fibropleural covering was essentially identical in each type. All grafts remained isodimensional in adult animals. No crimping or calcification occurred and the fabric remained pliable even after several months. Graft failure and complications were dependent more upon technical skill and familiarity with the peculiarities of plastic

TABLE V

FABRIC T-10

Dog No.	Diameter (cm.)	Length (cm.)	Postoperative Days	Thrombosis	Endothelium	Sterilization	Course
T-52...	0.8	3.7	90	0	10 mm.	Zephiran	Sacrificed
T-56...	1.0	4.1	6	0	None	Zephiran	Graft dehiscence
T-57...	0.8	3.5	202	0	Total	Zephiran	Sacrificed
T-58...	0.8	3.6	1	0	None	Zephiran	Hemorrhage at distal shunt tie
T-60...	0.8	4.5	365+	0	.....	Zephiran	Alive; femoral pulsation normal
T-61...	0.8	2.5	195	0	Total	Zephiran	Sacrificed
T-62...	1.0	4.5	38	0	None	Zephiran	Distemper
T-65...	1.0	7.5	1	+	None	Zephiran	Unwashed graft
T-66...	0.8	7.3	14	0	None	Autoclave	Distemper
T-67...	1.0	2.7	177	0	12 mm.	Autoclave	Sacrificed
T-68...	1.2	4.7	358	0	Total	Autoclave	Sacrificed
T-71...	1.0	11.5	365+	0	.....	Autoclave	Alive; femoral pulsation normal
T-75...	0.6	3.3	345	0	Total	Autoclave	Sacrificed
T-76...	1.0	4.5	167	0	Total	Autoclave	Sacrificed
T-73...	0.8	4.5	344	0	Total	Autoclave	Sacrificed
T-87...	1.0	4.0	63	0	4 mm.	Autoclave	Strangulated bowel
T-90...	1.2	6.5	321	0	Total	Autoclave	Sacrificed
T-92...	0.8	6.5	135	0	4 mm.	Autoclave	Sacrificed
T-94...	1.2	12.0	300+	0	.....	Autoclave	Alive; femoral pulsation normal
T-95...	1.2	6.0	133	0	Total	Autoclave	Sacrificed
T-96...	1.2	6.0	3	+	None	Autoclave	Thrombosis of proximal shunt tie
T-97...	0.8	5.5	3	0	None	Autoclave	Pulmonary hemorrhage
T-99...	1.0	3.5	123	0	12 mm.	Autoclave	Sacrificed

grafting than the type of graft fabric used. Of these three materials, T-8 appears to be the most ideal because of its great pliability and low porosity.

The method of sterilization, whether by soaking in zephiran or autoclaving, seems to be unimportant. There was no evidence of infection in any graft. No difference could be noted in the two groups regarding amount of fibrosis, rate or amount of fibrinous development or endothelial growth. Autoclaving was tolerated well by the teflon fabric, even when repeated six times. Repeated autoclaving did not change pliability, permeability nor porosity. Of those grafts subjected to an intraluminal pressure of 500 mm. Hg after autopsy, no disruption of the anastomosis or graft seam could be produced. Most of the vessels tested had grafts older than 300 days which would indicate that the strength of the fabric was unaltered by tissue fluids. Of the sixty animals having teflon plastic aortic grafts, fifty-five are considered to be satisfactory having either carried blood adequately till time of sacrifice, showed no unusual reaction nor thrombosis at the time of death from some other cause, or remained functioning as evidenced by normal femoral pulsations at this time. Three of the failures were with T-10 fabric and two with T-8. No failures were noted in T-3 nor with the last fifteen grafts done. One of the grafts dehisced along its longitudinal seam because the edge was trimmed too closely to the suture line. Four grafts were thrombosed at autopsy, two in each T-8 and T-10 fabric type. Two of these originated either proximal or distal to the graft in intimal tears caused by the crushing of the intima by the shunt ties. One was due to failure in washing the graft fabric with septisol and water in order to remove the oil or waxes of the weaving processes. No explanation can be given for the fourth graft thrombosis which occurred 154 days postoperatively in an endothelializing graft. Other early animal deaths were not related to the grafts but rather were due to the usual animal post-thoracotomy complications.

COMMENTS

While the rate of endothelialization and stabilization of the plastic fabric prosthesis is not completely predictable, the eventual results are highly satisfactory. The reasons for the variable growth of endothelium are not entirely clear, but it is suspected that the age of the host aorta is extremely important. In growing animals endothelialization was complete in six to twelve weeks. The average period in adult dogs for the lining to become totally smooth and translucent was six months.

The over-all graft success is 92 per cent in this series and 98 per cent when those cases due to obvious technical errors are excluded. This compares favorably with the initial work on Vinyon N in which patent grafts were found about 80 per cent of the time. Hufnagel reported about 90 per cent success with orlon fabric implanted in the thoracic aortas of dogs, and Deterling reports a similar success using nylon, dacron and orlon. Of equal importance is the fact that teflon exhibited neither a thick stenosing fibroplasia surrounding the graft nor calcific intimal deposits. These undesirable features are frequently seen in the grafts of other fabrics.

An important fact regarding the use of teflon as a prosthetic graft is the technical ease with which the material handles. It is soft and pliable, yet holds a crease firmly. The fibers are fine, of high tensile strength, and practically impenetrable. The fine needle of No. 00000 silk will pass as readily through the four thicknesses of the cuffed seam as it will through a single layer. The particular weaves chosen are tight enough to prevent ravelling or loosening from the cuffed ends. Furthermore, this material is procured easily and cheaply, can be stored and transported simply and, in addition, it can be adapted to any number of situations either preoperatively or during the progress of the operation. At operation, after a few measurements, it can be fabricated and sterilized by autoclave in less time and with considerably less effort than the reconstitution and preparation of a lyophilized homograft.

Aside from the difficulties of procurement, the time expenditure of personnel in processing, the cost and so forth of homografts, a major dissatisfaction stems from the problem at operation of finding a completely suitable specimen, either in diameter or shape, to bridge the resected area.

In an era in which surgeons are concerned not only with the problems of individual patients but also with the problems of mass casualties and logistics, the value of a satisfactory prosthetic vascular graft becomes apparent. Because of the continued interest of many

investigators, important progress has been made toward this end.

CONCLUSIONS

1. Teflon fabric (T-3, T-8 and T-10) is chemically inert, non-wettable, exhibits high tensile strength and low porosity, and is obtainable in a smooth taffeta weave. This fabric is inexpensive, easily procurable, simply fabricated, and easily sutured, sterilized and stored. Consequently, it would appear to be highly adaptable as an arterial prosthesis.

2. Teflon fabrics were successfully substituted for portions of the thoracic and abdominal aorta in sixty dogs with a 98 per cent patency. Some animals were observed for more than one year.

3. Of five failures (thromboses or rupture), four were due to obvious technical errors. In only one instance could the failure be attributed to the graft (2 per cent).

4. The inner side becomes covered by an endothelial-like membrane. No excessive fibrosis occurred externally. No calcification was noted in any instance.

5. Some grafts implanted over six months were tested for "bursting strength." Pressures over 500 mm. Hg did not result in a single rupture.

6. Of the three fabrics tested, T-8 is preferred but has no major advantage over the others.

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DISCUSSION

Roland D. Pinkham (Seattle, Wash.): The use of synthetic prosthetic material for blood vessel replacement certainly should continue to be a stimulating and challenging surgical problem for some time to come. Since the days of Carrel, surgeons have dreamed and speculated on the possibilities afforded by vascular substitutes. At long last it would appear we are approaching that time. The vascular substitutes are still to be considered in their experimental phases; it is quite evident that the clinical usage of these substitutes cannot await detailed experimental validation. It is therefore increasingly important that we learn as much as we can about these substances from the experimental laboratory as rapidly as we can.

With the wave of enthusiasm for synthetic vascular substitutes the use of the homograft should not be discredited entirely. It still has much to commend it, and perhaps in time more will be learned so that the ease of procuring and processing vascular grafts will improve.

The authors are indeed correct in stating that the main attributes of artificial replacements should be availability and ease of handling. These features will become more significant as the need for arterial replacement increases.

It would appear that the main cause of failure with these substitutes is due primarily to intraluminal thrombosis. The critical size of the vessel grafted, which is prone to thrombose, varies slightly with the various materials employed. In general, it can be assumed that about 50 per cent will thrombose regardless of the materials heretofore used, providing the diameter of the vessel replaced is 6 to 7 mm. or less, whereas most substitutes will remain patent if the vessel diameter is 9 mm. or over.

It becomes readily apparent that both the physical and physiologic properties of teflon render this material superior to those substances previously

described. I am mindful, however, that the technical abilities of the authors were in no small way responsible for their excellent results. The low incidence of thrombosis in small arteries, in their experience, may largely be due to their technic rather than to the physical properties of teflon. Undoubtedly other materials will be introduced in time which more nearly approach the ideal, but for the present it would appear that teflon promises to be a real contribution and should be given clinical trial.

GEORGE GIRVIN (closing): I agree that it is going to take some time and further work with the use of these materials before we reach a solution that is universally satisfactory. However, we are very encouraged with our study so far in the use of teflon, which is probably the ultimate in inertness of the plastic materials.

Selection and Preparation of Fabric for Blood Vessel Grafts

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Supported by Research Grants from the Oregon Heart Association, with the assistance of the Department of Surgery of the University of Oregon Medical School, Portland, Oregon.

Much misinformation, or at least careless advice, has been given about obtaining cloth suitable for fashioning blood vessel grafts. The frequently heard suggestion "go to the nearest department store" probably represents the worst possible advice to the surgeon who requires fabric for a graft. Personal experience of the authors indicates a deplorable lack of knowledge or interest in the structure, and particularly the porosity of the fabric, on the part of clerks, supervisors, buyers and even wholesale merchants. This detailed information, which is so vital in selecting suitable fabric, can be obtained only from the factories, many of which are not interested in supplying only a few yards of cloth. Unless one can obtain plastic fabric with a known porosity of less than 50, as recommended by Deterling and Bhonsley,[1] considerable hemorrhage and possible mortality can be avoided by rendering the unknown or porous material impervious to leakage by coating it with polyethylene.

Repeated animal research experiments during the past eighteen months have indicated certain advantages from coating porous plastic fabric blood vessel grafts with polyethylene. The principal advantage is represented by absence of initial blood leakage through the porous fabric during the first few seconds or minutes before clotting occurs. Obviously this prevention of blood loss avoids the necessity for excess blood replacement, eliminates the need for reclamping the vessel and prolonging the period of occlusion, and reduces the possibility of a period of hypotension with attendant thrombus formation and later emboli.

The impervious polyethylene covering also permits moistening the graft with a heparin solution during its insertion to avoid the formation of clots within the graft before the occluding clamps are removed.

Certain technical advantages are present in the preparation and insertion of the graft in that the polyethylene prevents fraying of the edges of the cloth, permitting a narrower inverted cuff at the ends and narrower margins without pinking along the seams. A slight technical disadvantage is the increased thickness and stiffness of the fabric covered with polyethylene in comparison with thin fabric.

The polyethylene-covered fabric graft was prepared by the following method:

A thin orlon fabric with a high thread count (warp 160, filling 123, porosity 124.4, thickness .0069) was impregnated with polyethylene on one side in the following manner: A sheet of thin polyethylene film was placed over a sheet of orlon fabric about 8½ by 11 inches in size. This was covered with a sheet of cellophane and pressed with an electric iron set at the proper temperature for nylon. The cellophane covering was required to prevent the iron from adhering to the polyethylene which melts at 120°C. The polyethylene sheet became loosely adherent to the orlon but additional heat was required to fuse the two sheets sufficiently to permit handling, stitching and sterilization. This was accomplished by autoclaving the loosely adherent fabric and polyethylene still covered with cellophane between folded towels. This differs from the technic recommended by Shumacker et al.[2] only in that they suggested placing a layer of polyethylene film between two layers of nylon fabric which would increase the thickness of the final product by one-third and make it more bulky to fold and suture.

The disadvantages of porous plastic fabric without polyethylene covering were demon-

strated by experimental work on eleven dogs, in which sections of the thoracic aorta were replaced with orlon fabric grafts. Shunts of polyethylene tubing with flanged ends were used through the graft during its insertion. A slight leakage around the intraluminal shunts from adjacent intercostal vessels filled the graft with clots, requiring the local use of heparin in the graft and in the temporary shunt during their insertion.

Despite the local use of protamine, pressure on the grafts and gradual removal of the lower clamp first considerable initial blood loss occurred which required reclamping and a delay of several minutes until clotting began in the cloth. Eleven dogs with porous orlon grafts all died during the first eighteen hours postoperatively, apparently due to the immediate or late results of hypotension from initial blood loss through the graft. All of the dogs were autopsied and no excess blood was found in the thorax to indicate continued bleeding in any instance. Two dogs in which thin porous orlon grafts impregnated with polyethylene were used in the thoracic aorta had no initial leakage and survived the operation for two and six months, respectively, until they were sacrificed.

Admittedly, these dogs were subjected to several severe disadvantages not present in a hospital operating room and not present in operations on the abdominal aorta. No transfusions or intravenous fluids were used for blood replacement. Prolonged basal nembutal® anesthesia was used in most cases with intermittent blasts of compressed air through a small intratracheal catheter to maintain partial expansion of the lungs and a poor degree of oxygenation.

The poor oxygen saturation of the blood would greatly accentuate the effect of relative anemia in these animals. The choice of the thoracic rather than the abdominal aorta for replacement created additional problems in requiring a shunt to maintain the renal circulation during the anastomosis. This shunt in turn required the use of heparin which increased the bleeding tendency and prevented the use of pre-clotting technics.

Insertion of grafts of orlon fabric of intermediate thickness with a porosity of 55 was made in the abdominal aortas of additional dogs with a moderate amount of leakage. Blood loss was much less marked and disastrous than through the lighter fabric with a porosity of 124 but was still sufficient to make its use objectionable without a polyethylene covering. (Table 1.)

Grafts of much heavier, less porous orlon (porosity 11.2) were inserted without any leakage despite a considerably lower thread count. This orlon fabric (No. A10,037) is recommended for the preparation of blood vessel grafts without the necessity of adding a polyethylene covering. Cauterization of the cut ends is used in place of cuffs on grafts of smaller caliber due to the thickness of the fabric. The cauterized edges of this fabric have shown a greater ability to hold stitches than nylon filter fabric, making it safer to use without a cuff. (Fig. 1.)

TABLE 1
COMPARISON OF THE DIFFERENT TYPES OF ORLON FABRIC*

Quality Number	Warp	Filling	Porosity	Thickness	Result
A10,037	101	43	11.2	.0127	No leakage
A10,027	72	53	54.6	.0083	Moderate leakage
A10,100	160	81	124.4	.0069	Severe leakage

* Supplied by Stern & Stern Textiles, Inc., Huguet Fabrics Division, Hornell, N. Y.
† Recommended.

AUTOPSY FINDINGS

Examination of dogs Nos. 1 to 11 showed no evidence of late blood loss either through or around the graft in any case. Both surfaces of the fabric were covered with a smooth glistening layer of fibrin. The aortas contained long, stringy clots both above and below the grafts. The clots were not firmly attached to the grafts in any instance to suggest antemortem obstruction by thrombosis.

Examination of dog No. 13, sacrificed two months after operation, showed the grafted area to be surrounded by scar tissue with approximately 1 or 2 cc. of clear fluid around the polyethylene which had partially separated from the orlon. The inside surface of the graft was covered with a layer of fibrous and fibrinous tissue which was fairly uniform, indicating that it had not grown in from the ends but apparently started from multiple different areas over the inner surface of the graft. The tissue could not have grown through the fabric as suggested by Sauvage and Wasalowski[3] due to the impervious polyethylene around the outside. (Fig. 2.)

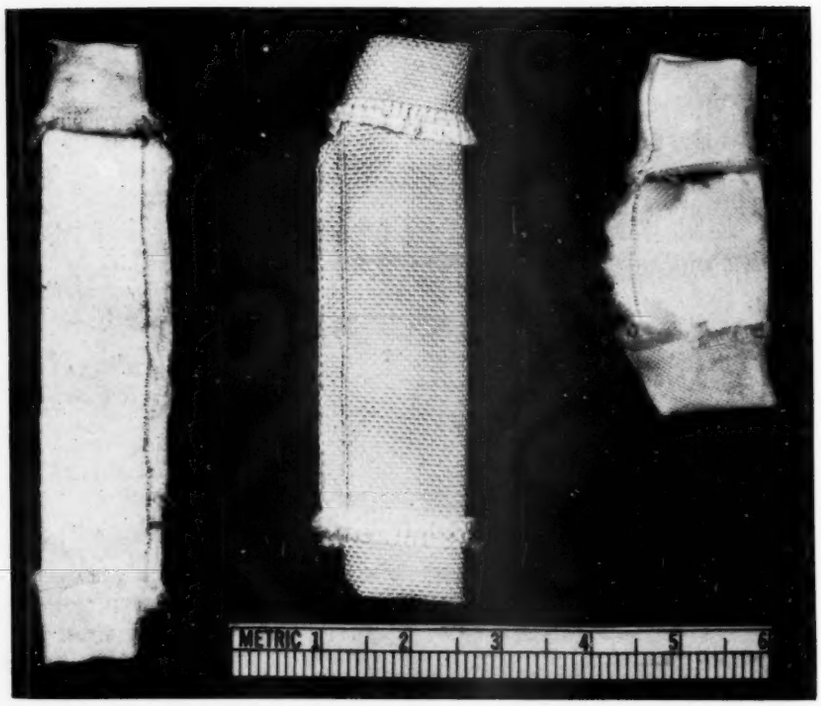

FIG. 1. Orlon fabric grafts: *left*, porous fabric covered with polyethylene; *middle*, heavier fabric with low porosity which requires no polyethylene covering to prevent leakage; *right*, porous fabric without polyethylene covering which caused 100 per cent mortality from leakage.

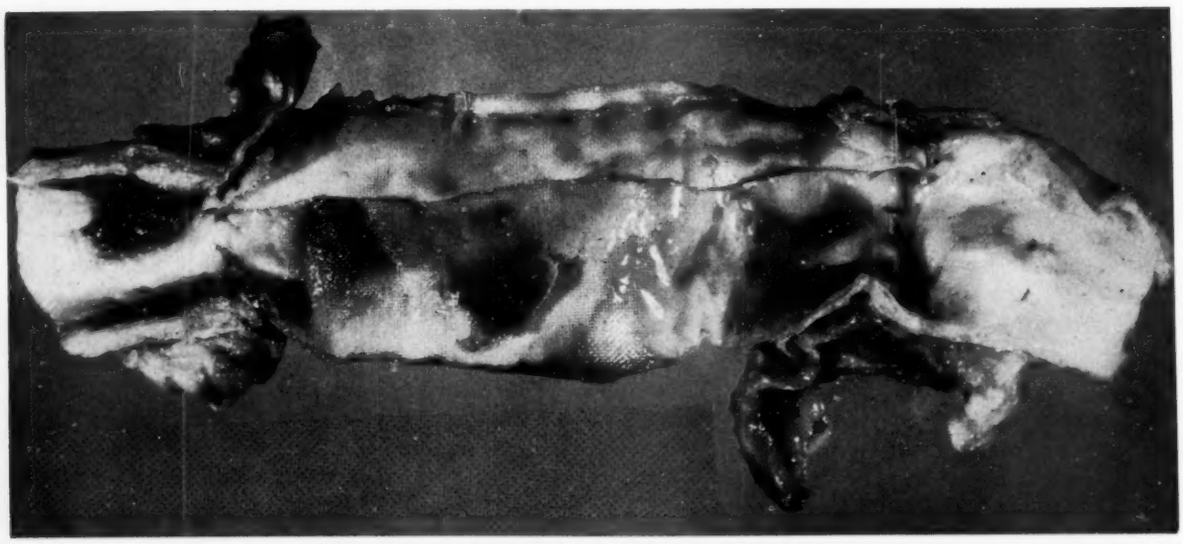

FIG. 2. Polyethylene-covered fabric graft two months postoperatively, showing fabric mesh through thin layer of fibrous tissue.

Examination of dog No. 12, sacrificed six months after operation, showed the grafted area to be embedded in dense scar tissue attached firmly to the graft without any intervening fluid. There was no evidence of any separation of the polyethylene from the graft, although it could be separated by blunt dissection after opening the graft longitudinally. The inside of the graft showed approximately 75 per cent of the surface covered with firm, glistening

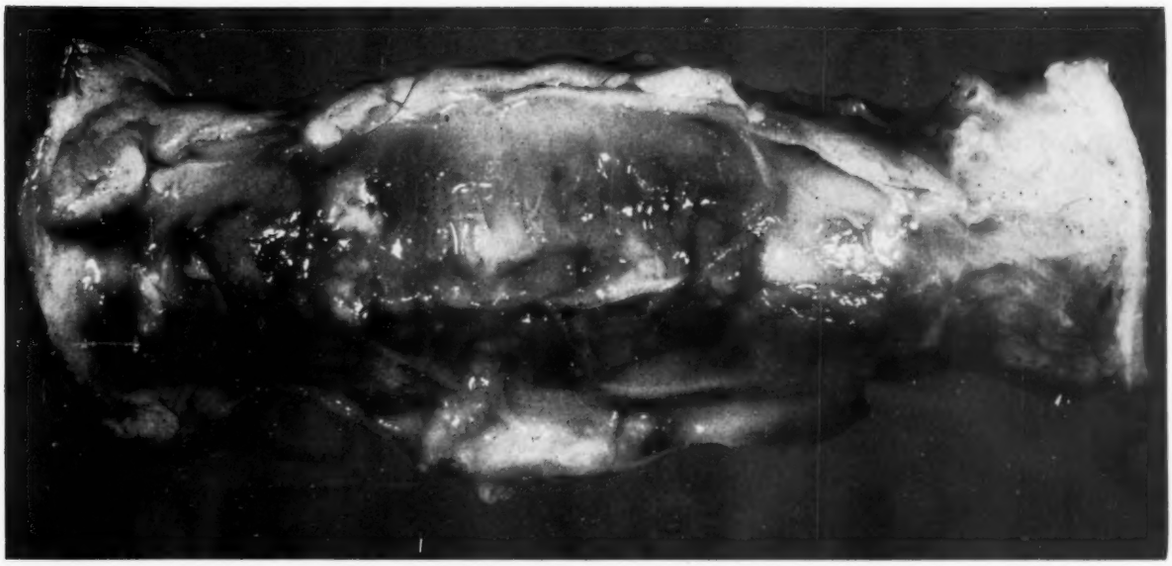

FIG. 3. Polyethylene-covered fabric graft six months postoperatively, showing thick layer of smooth fibrous tissue uniformly covering inside and outside of graft.

white fibrous tissue and the other 25 per cent covered with pink fibrinous and fibrous tissue. (Fig. 3.)

REMARKS

The multitude of suggestions which have been made regarding the control of the initial oozing suggests that this represents a frequent problem. The recommendations for control of initial oozing seem to fall into two groups, namely, one relating to selection of special types of fabric[1,10] and the other relating to the preparation and application of the fabric.[2,5]

The criteria for proper selection of the most suitable type of fabric has been described best by Deterling and Bhonsley[1] with detailed descriptions of many different types, stressing the most important qualities, namely, type of weave, surface texture, thickness and porosity. A fabric with an air porosity of less than 50 was recommended as the most reliable criterion in selecting fabric which prevents initial oozing. Porosity depends directly upon the size of the interspaces between the threads and is not necessarily controlled by the thread count, but is influenced much more by the looseness of the twist of the thread in the filler (woof) fiber. The denier, or number of filaments in a thread, is of less importance than the looseness of the twist. Calendering, or the application of heat and pressure, decreased the porosity of orlon and dacron. Autoclaving has been recommended[8] as another method of decreasing porosity by additional shrinkage of the fibers.

Early attempts at procurement of these special types proved somewhat discouraging, primarily due to a lack of interest among the large manufacturers in making or dispensing a few yards of these special fabrics following uniform specifications. Some of the special weaves which were recommended by previous investigators already had been discontinued by the manufacturers.[8] The identification of other fabrics which were still under investigation could not be divulged, as was deplored recently in an editorial by Creech.[6]

Special preparation of the fabric to prevent oozing has included the application of substances such as lucite, silicone[5] and paraffin,[7] etc., to the fabric and pre-clotting by soaking the graft in fresh blood immediately before its insertion. The latter method of pre-clotting proved unsatisfactory in this series due to the required use of heparin in and around the vascular shunt. The former methods have been reported as having caused early or late complications from tissue reactions apparently due to the additional substances.

Probably the most important step in the preparation of fabric for grafts is to wash, rewash and rinse the fabric very thoroughly with detergents to remove the irritating soluble substances left by the manufacturing process which tend to produce clotting and thrombus

formation. Hufnagel[5] admits difficulties with thrombus formation in unwashed fabric, and Harris and co-workers'[10] comparisons of thrombus formation caused by different types of fabrics, including polyethylene-covered nylon, could be considered as invalid due to lack of preliminary washing of the fabrics. Tapp[9] considers ordinary detergents inadequate and recommends washing all fabrics with ether.

The outstanding improvement in survival rates of these dogs resulting from the application of a sheet of polyethylene around the thin fabric indicates a distinct advantage to be derived from the use of this combination in comparison with the use of fabric with a high or unknown porosity. This type of polyethylene-covered graft has been used successfully by the authors in the human aorta. Objections have been made[7] to the use of polyethylene around fabric grafts claiming that the polyethylene acts as a barrier to the growth of fibroblasts from the outside and retards tissue covering of the inside, as well as creating an undue tissue reaction with accumulation of fluid around the graft. These experiments, although few in number and extending for only a six-month period, indicate that the late results are quite satisfactory, with dense fibrous tissue inside and outside the graft.

The addition of polyethylene makes it possible to employ a wider variety of plastic fabrics in case special types with a known low porosity are not immediately available. This is not intended to indicate that a polyethylene-covered fabric graft is superior to one fashioned from a properly selected fabric with a low porosity, but it is superior to one which has a high or unknown porosity.

CONCLUSIONS

1. The addition of a polyethylene covering around the outside of thin porous fabric grafts converted a 100 per cent mortality to a 100 per cent survival in this series of experiments.

2. Polyethylene prevents the initial oozing through the fabric grafts with attendant blood loss and shock, which apparently was the cause of death in the dogs in which porous fabric had been used.

3. The presence of the polyethylene around the graft did not appear to prevent complete covering of both internal and external surfaces with fibrous tissue.

4. Certain technical advantages are provided by the polyethylene covering in preparation and insertion of the graft.

5. Procurement of special fabrics becomes less essential when polyethylene is added to make it impervious to initial leakage.

6. The technic for preparation of the polyethylene-covered fabric is described.

7. Orlon fabric with a porosity of 11.2 required no polyethylene covering to prevent initial oozing, and is recommended for the preparation of arterial grafts.

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DISCUSSION

Frank Gerbode (San Francisco, Calif.): My own experience with the use of prostheses in blood vessel grafts is extremely limited because I have always preferred using homografts or in medium-sized peripheral vessels autogenous vein grafts. However, there is a great need for continuing research in synthetic materials, for biologic grafting material does not supply all our needs; it is highly likely if the proper material is found that, at least for abdominal aneurysms, replacement by synthetic material could be desirable.

As to impregnating plastic fabric with polyethylene, it strikes me as a very poor way to gain any advantage. In fact, it poses a considerable disadvantage in that it should prevent growth of con-

nective tissue into the fabric. This growth would seem quite desirable to guarantee a firm biologic tube based upon a network of plastic fibers.

It is my belief that we have not fully exploited the possibility of obtaining homografts, and that more time and effort should be expended in establishing artery banks in large communities where it may be possible to obtain the vessels from fresh necropsy material. This has the advantage of standardization and uniformity which is desirable.

HANS H. ZINSSER (Los Angeles, Calif.): I am interested in these papers and believe the two basic points which must be brought out in regard to both of them are that, first, we are essentially attempting to replace very little more than a hole, a long hole which goes in the right direction and does not leak. The other capacities of this arterial continuity are essentially wide open. Second, we want no early tissue reactions that will be immediately unfavorable to the animal, and no long-term reactions.

In a recent discussion with the research section of one of the plastic companies it was apparent that they are totally uninterested in the clinical development of any material because of the idea that all materials are liable to produce sarcoma. They are delighted to give doctors samples of anything they want as long as the doctors do not tell the company what they do with them. The company does not want to be implicated in any way whatsoever.

We are reasonably certain that homografts will not have this type of long-term reaction. There are, however, enough proved instances of long-term failure of homografts from the point of view of calcification and excessive fibroblast overgrowth that make it necessary for us to continue to look for other substances.

From the analogy of the structure of the fibrous components of the aortic wall we have been struck with the suitability of various felts. Two felt companies have been good enough to attempt to do something they have never done before, namely, make tubes of felt, which I think will now be available. Apparently it is cheaper to make felt washers by making tubes first; the companies have never realized this before. These felt tubes are nice in several ways. (I want to put in an aside now on the arrangement of the fibers in the fabrics with which one would like to make a graft. If the material is stitched so that the fibers are run diagonally, one obtains a considerably pleasanter feel to the graft. Some of the difficulties of unraveling at the edges are solved by the fact that the stresses are rather evenly distributed at the sutures by having the weave diagonal. One does get stretch in both directions. Deterling made this point and credited it to Dr. Hufnagel. I like to think Dr. Hufnagel was quoting us in turn from previous conversations a while back.) Felts have no definite weave, as the fibers are randomly arranged. The first 2 or 3 per cent extension is the most important portion of the elasticity of vascular replacement. Felts have excellent properties in this region as far as lack of permanent stretch, that is, the give is instantly returned. I think something can be done with extending such types of felts. We have used some wool felts but they have bad tissue characteristics. As far as fibroblast growth, it is rapid in ordinary wool felt, but these can be coated with material much like teflon but with lower molecular weights so as to remain fluid. We have waxes and oils which can be mixed to get appropriate melting points. Some are semi-solid at body temperature and have excellent damping properties. As far as tissue reaction around the felts used in a few dogs, I do not believe our technical results are worth talking about yet.

I think one should retain the emphasis on the concept that we are trying to produce a long hole with elastic properties to match the vessel we are replacing. There is no point in putting a very flexible or flabby replacement into a very stiff aorta. At the two ends the transmission properties of the replacement are such that we can expect undue stresses at the ends of the replacement.

J. KARL POPPE (closing): I wish to thank the discussers for their various remarks. At the time our experimental work was started blood vessel grafts were needed and none were available. A few different types of fabrics were tested before using them and were found to be quite unsatisfactory. It was then that the more extensive experimental work originated.

Only two animals were used in which polyethylene-covered fabric grafts were employed. Admittedly that is a small number, but it seemed sufficient to prove that initial bleeding was controlled, which was the purpose of the project.

Dr. Gerbode's interest and discussion were much appreciated. First, in regard to the difficulty with the impervious grafts which will not permit growth of fibroblasts, I recognize that as a general topic of conjecture and discussion and some alarm, although impervious grafts have been used for several years and have been covered with fibrous tissue. Hufnagel reported six years ago that the inside of his rigid methyl methacrylate tubes became covered with an intima-like material within a few weeks.

Shoemaker's work also indicated that the inside of the polyethylene-coated graft was covered with a thin, fibrous layer similar to that in the examples shown here. I again bring out the point that this did not appear to grow in from the edges, but rather to start simultaneously in many different areas.

In regard to the question about the preferable qualities of homografts, I might mention again Merendino's work with several hundred pigs in which homografts were somewhat disappointing in

view of the numerous sclerotic changes with stenosis or dilatation. Waslowsky also found essentially the same thing to apply in his several hundred pigs and other animals. The only satisfactory grafts were autografts, but they are not entirely practical. Unfavorable findings were reported as being particularly prominent in the freeze-dried method of preparation of homografts, with a great deal more sclerotic changes in this group than in the fresh homografts.

I am sure we still do not have the complete answer to this, but dry-frozen homografts seem to have a number of the same disadvantages, if not more, than the plastic fabrics.

Vascular Grafting in the Replacement of Arterial Aneurysms and Occlusive Disease

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THE attraction of vascular grafting in the treatment of arterial disease is its approach to specificity. Direct surgical intervention in vascular conditions heretofore has been infrequent. The surgeon usually has been limited to an indirect approach or one of palliation. Now there is hope for relatively long term relief by replacement of diseased arterial segments.

Therapy for afflictions of arteries, aneurysmal dilatation or occlusions usually has entailed considerable surgical ingenuity, but it always has been disappointing and short of the theoretic ideal. The dilated artery has been treated by attempting to reinforce its wall or by attempting to limit the lumen within the dilatation in such a manner that inevitable rupture might be forestalled. Sometimes the artery could be dispensed with entirely by excision or by obliteration. These methods not infrequently demand considerable courage, but they never genuinely satisfy either the local situation or the desire of the surgeon to do an effective job. For obliterative disease there was equally little opportunity for direct intervention. Sympathetic denervation made up the principal armamentarium until the recent development of thromboendarterectomy and graft replacement. Sympathectomy has a truly rational physiologic basis only in Raynaud's disease and related vasospastic disorders. For the bulk of obliterative disease the indication always has been somewhat empiric and certainly indirect. This does not condemn sympathectomy, an immensely useful procedure in peripheral vascular problems, but it does acknowledge a primary defect in the operation which hardly can be overlooked when one considers the broad problem of obliterative vascular disease.

Among the questions facing those who would use grafts in surgical practice is the selection of the proper material. Autogenous veins and arteries provide a sharply limited source. Homologous arteries or synthetics remain the most useful materials. It was the opinion of the authors in a small program devoted entirely to private practice that we should become familiar with the advantages and limitations of a single type of graft rather than gain scanty experience with a wider variety of substances. We believed that homografts were the most versatile and most likely to meet our needs despite the difficulties in procuring them. The Washington State Heart Association has established a bank in which homologous arterial segments are preserved by the freeze-dry method[2,5] and are then available to all surgeons in the state of Washington insofar as supply will meet demand. We have had the good fortune to be concerned with the establishment and maintenance of that bank. We therefore have concentrated our efforts on the use of homologous segments; we have virtually no experience with synthetics. Our use of autogenous vein grafts is limited to a few instances before arterial grafts were available.

Evaluation of risk is difficult as one contemplates vascular replacement. It should be nothing but a surgical truism to declare that an aneurysm of the abdominal aorta, for example, inevitably will cause a patient's death within a short time. A few of the statistical studies[9] which have been collected tend to support that view. Further analysis[2] introduces a number of factors, however, which must be remembered. It is often extremely difficult to determine how long a patient has had an aneurysm. Several in our small series were detected only at the time of laparotomy for other conditions. The patients had been asymptomatic, and their aneurysmal bulges were sufficiently inconspicuous so that routine physical examination

did not disclose many of them. Certainly that must be common among patients with small abdominal aneurysms. A number of the patients are elderly and have serious concommitant disease in the cardiovascular system and elsewhere. Many die from related causes but not primarily from rupture of an aneurysm. Prognosis is extremely difficult and must be made cautiously even when a surgeon feels enthusiasm for ridding the patient of his most obviously dangerous lesion.

Obliterative disease of the arteries likewise constitutes a hard problem for appraisal. Undoubtedly there are many people throughout the country with relatively serious arterial insufficiency who suffer minor degrees of incapacity for long periods before they seek medical attention. Histories are often quite vague. Many patients learn to regulate their activity in such a manner that a circulatory bed of diminishing capacity is not evident because of the decreased demand as they tailor their activities to their peripheral circulation. Other patients react violently to a limitation of their exercise tolerance and seem almost through resentment to increase their physiologic needs. Some of the patients would appear to be suffering primarily from a deficit of blood supply to muscle; others become involved seriously in circulatory insufficiency to the skin. Often it is extremely difficult to assign the precise deficit to the organ involved. This whole matter becomes further complicated in trying to evaluate the results of conventional therapy for obliterative disease. One who would investigate sympathectomy as a therapeutic agent must decide about salvage of limbs and also about patient mortality. The problem is further colored by the morbidity of sympathectomy. It is the opinion of the authors that this procedure involves a great deal of pain postoperatively and that many patients suffer marked invalidism for varying periods after surgery regardless of the care with which the procedure is performed. Paresthesias and neuritis are not infrequent results of sympathectomy; they occur with almost alarming regularity. None of these complications argues against the use of sympathectomy as a therapeutic tool if no other procedure is available, but they have stimulated investigators to search for improved methods such as graft replacement.

It behooves the surgeon who changes from a procedure that he understands and can exploit to a new one of greater theoretic advantage to be sure that he does not greatly increase the risk. Such is the problem of anyone embarking on a program of vascular grafting. The grafting procedures are long and tedious and are technically exacting. Therefore, they demand a great deal of both the patient and the surgeon. The consequences of major error in either selection of patients or in technical performance can be disastrous since they can involve the loss of a patient's limb or his life.

With these factors in mind and with the realization that our patients must not be subjected even to hospitalization which is unnecessarily prolonged, let alone to the consequences of serious failure, we elected initially to confine our grafting efforts to patients who had aneurysms in the abdominal aorta.[6] It was our hope thereby to acquire technical skill and to eliminate error before attacking obstructive lesions intrinsically more benign and in which failure would be more regrettable.

Six abdominal aortic aneurysms have been resected. The patient's ages varied from thirty-eight to sixty-four. The longest interval since operation is two and a half years. All the survivors have a satisfactory result in terms of comfort, lack of any measurable recurrence of their aneurysms, and satisfactory blood flow to their legs. Of the three who died, only one represents a straight operative failure. This patient, a fifty-eight year old man, had a medium-sized aneurysm associated with pain in the buttocks and thighs. At operation almost complete thrombosis of the aneurysm was found. At the conclusion of surgery, before the abdomen was closed, it was believed that he had excellent pulsations through the graft and downward into the iliac vessels. About four hours postoperatively, however, it was evident that thrombosis of the femoral vessels along with the graft and the iliac arteries had occurred. An effort was made to enter the femoral vessels and to aspirate the thrombus with the hope that circulation might be restored. Nothing was accomplished. It was our early judgement that a patient would not tolerate re-exploration and re-establishment of a satisfactorily functioning graft. We now have come to the conclusion that if the graft gives indication of thrombosis, the only thing to do is to reoperate in the primary area of operation.

Another death occurred from cardiac arrest

about an hour after surgery. The patient, who had had a ruptured aneurysm for approximately fourteen hours before surgery, was taken to the operating room with a systolic blood pressure which never exceeded 60 mm. of mercury despite massive transfusions. We were able to resect the aneurysm and to insert a graft that was functioning satisfactorily at the time the abdomen was closed and which continued to function until his death. He had had a previous coronary occlusion.

AORTIC ANEURYSM

	SEX	AGE	PREV. HISTORY	RESULTS
	♂	48		Operative failure—thrombosis of graft
	♀	38	Aneurysm wrapped c cellophane 5 yr. ago	Well
	♂	62		Died 6 wks. P.O. of bleeding ulcer
	♂	51		Well
	♂	54		Died 2 hr. P.O.* but graft patent
	♂	55		Well

*Cardiac arrest

FIG. 1. Grafts for abdominal aneurysms.

The third patient lived approximately four weeks following surgery with an excellent local result. He died as a result of massive gastrointestinal hemorrhage from a marginal ulcer at the site of a previously performed gastroenterostomy. Unfortunately we did not know about this occurrence until after the man had died. His graft was found to be in satisfactory condition at autopsy.

One of the three patients who survived, with good results, was a relatively young woman who had had an aneurysm wrapped with reactive cellophane five years before coming to us, but who required resection and a graft because the lesion was beginning to expand and cause pain. (Fig. 1.)

Obliterative arterial disease usually presents a less dramatic demand for vessel grafting.[7,10] The patients come to the surgeon's attention for discomfort rather than with any sense of imminent disaster as, for example, from perforation of an aneurysm. They also have available to them the benefits of sympathectomy which has an established place in the treatment of occlusive disease and which is accepted despite its limitations. For that reason it is more difficult to start treatment for the occlusive lesions. One dislikes the possibility of operative failure here even more than in aneurysms.

The Leriche syndrome arising from thrombosis of the lower aorta and the upper iliac vessels constitutes the outstanding example of an occlusive disease in which grafting is desirable. It has been shown clinically and experimentally[1] that sympathectomy does not offer a great deal for terminal aortic occlusions as well as for occlusion of the iliac vessels. This lesion not uncommonly occurs in younger men than does the more generalized arteriosclerosis of peripheral vessels in older patients. The patients with aortic occlusion are relatively vigorous and young but have a crippling lesion; they are in real need of help. There are, however, certain criteria which apply to all successful grafts and these become increasingly strict as vessel size decreases. They are as follows: (1) the graft must remain patent; (2) it must have an adequate supply of blood at its proximal end or source; and (3) it must have a sufficient path of egress at its termination or distal end. Failure to meet any or all of these conditions will result in thrombosis of the graft and operative failure of varying degree. Beyond the popliteal level, arteries are too small for practical application of grafting technics. It has been found by Linton[10,11] and Crawford et al.[4] that employing an end-to-side technic, in which the end of the graft is attached to the side of the host vessel, facilitates the operation

LERICHE SYNDROMES

	SEX	AGE	RESULTS
	♂	66	Died 8 days P.O.
	♂	55	Well
	♂	53	"
	♂	47	"
	♂	42	"

FIG. 2. Grafts for occlusion of the abdominal aorta and iliac arteries.

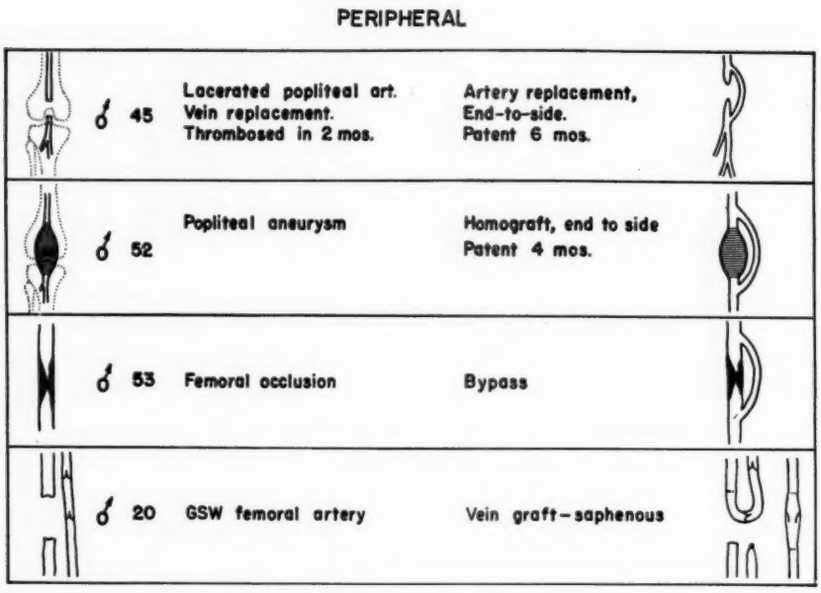

FIG. 3. Grafts to peripheral arteries.

in smaller vessels. Patency seems to be maintained more readily. This probably is because the circular muscles of the host arterial wall tend to hold open a lateral incision in the artery while the same muscle fibers constrict the open end of a vessel which is transected cleanly across. It also is easy to appreciate the fact that end-to-end anastomosis may fail from an actual constriction at the anastomotic site because of the vessel which is used up in the cuff.

Our series of aortic bifurcation grafts for occlusion is limited to six cases, the earliest done almost a year ago. The ages of the patients have varied between forty-two and sixty-two. All have been men, and in all but one the results have been encouraging. Our one complete failure was a sixty-two year old man. Uncritical appraisal of his aortogram and a failure to appreciate adequately his generalized arteriosclerosis resulted in loss of both his legs, and he died about ten days after surgery. In retrospect, it seems that the sound principle which was contravened here was that of failure to obtain satisfactory outflow from the graft. The external iliac vessels into which the graft was implanted by end-to-side technic were inadequate. Repeated efforts to establish blood flow through the iliac vessels never were entirely satisfactory, although the vessels seemed to be pulsating at the conclusion of the operation.

Good results from aortic bifurcation replacement are most pleasing. For example, one of our patients, an engineer, spends most of his time at his desk but occasionally must make inspection trips out into the field. He is delighted with the improvement in his exercise tolerance since he has increased his claudication level from about 100 yards to almost 2 miles. This is the sort of result for which one strives and the kind for which one is willing to accept operative risk. (Fig. 2.)

Arterial homografts have proved useful to us in peripheral vessels in the three following patients.

A man of forty-five was injured in an accident in the woods at which time a sharp splinter from the butt of a log entered the popliteal space and severed the popliteal artery. Numerous attempts were made in a neighboring city to effect end-to-end anastomosis of the popliteal artery, with the unfortunate complication of thrombosis on the five occasions when the vessel was sutured. It was necessary for us to employ an autogenous vein graft in order to establish continuity and also to provide enough length of the vessel so that the patient might extend his leg to the normal degree. At that time no homologous arterial grafts were available. An arteriogram approximately one month after the placement of the venous autograft demonstrated patency in the vessel. It is believed that this graft remained

open for approximately three months before occlusion occurred. The patient's foot and leg did not have to be amputated, but he had pain constantly and could not walk or work. He was lost to follow-up but returned about fourteen months later for appraisal of the unsatisfactory result. Fifteen months after placement of the venous graft a homologous arterial graft was used as a by-pass procedure around the thrombosed graft. That technic has given him a satisfactory result for the last seven months. He now has pulsations at the dorsalis pedis and posterior tibial level, and his foot is improving steadily.

The second of the peripheral cases is relatively typical of the by-pass arrangement advocated by Crawford[4] and also by Linton[10] for peripheral segmental arteriosclerotic obstruction. The patient, a fifty-three year old man with calf claudication on the right side, was unable to follow his occupation as a real estate salesman because he tired as he took clients even on short trips about small residential properties. He has had an excellent result in terms of return of pulses to the ankles, and has great comfort in walking since the femoral obstruction was by-passed with a homologous arterial segment.

The third of these patients, a fifty-three year old physician, has provided us with an opportunity to compare methods of therapy in that he now has been treated for bilateral aneurysms in the popliteal arteries. He first came to our attention because of an acute occlusion in the left leg, probably from detachment of a mural thrombus from the popliteal aneurysm. Grafts were not available to use at that time so it was essential that we perform obliterative endoaneurysmorrhaphy and sympathectomy. The foot and leg were saved, but only after much pain and considerable desquamation of the toes, and the patient's complete incapacity to work for a period of approximately seven months. He had no pulses in the posterior tibial or dorsalis pedis arteries at the left ankle. He returned to us because of concern over possible accident to the right leg. It was necessary to perform another obliterative endoaneurysmorrhaphy on the right side because of the large size of the aneurysm. We believed that it could not be excised without danger to adjacent structures. This time, however, a by-passing homologous arterial graft was inserted, with an immediate satisfactory functional result. There are pulsations at the right angkle. The leg treated by the graft has never given him any discomfort, and it affords him more use as the stronger of his two legs. (Fig. 3.)

CONCLUSION

Excision with grafting appears to be a preferential treatment for aneurysms and is successful when applied with discrimination to the treatment of occlusive arterial disease.

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DISCUSSION

Ross Robertson (Vancouver, B. C.): The authors have made their points well, and I find myself in the fortunate position of being able to agree with them completely. It is only necessary then to re-emphasize what has been said in the

light of our experiences in Vancouver, and of course, to take the opportunity to give some of our own results.

Two of our men have been searching for the best material for the replacement of arteries. Dr. Peter Allen has replaced the abdominal aorta of dogs with autogenous vena cava supported by nylon mesh. An aortogram taken one year after operation showed that the graft was functioning well. The dog appeared normal with no apparent disability from loss of his vena cava.

The dog was then destroyed and a specimen was obtained. Its condition was excellent, and end to side anastomosis with the aorta was noted.

A photomicrograph of the graft showed the nylon mesh embedded in vascular connective tissue, viable muscle in the media and a normal intima.

Dr. Allen naturally believes that this is the best material for arterial replacement and we are inclined to agree. However, thus far, none of us have felt justified in sacrificing the vena cava of a human patient.

Dr. Allan McKenzie has experimented with various synthetic materials and has come to agree with Dr. Crystal's selection. He puts it this way, "No synthetic material we have tried approaches the physical qualifications of the homograft. It is a subtle combination which is hard to match: smooth lining, elastic, permeable but not too permeable, tough but not hard."

He has organized a blood vessel bank and preserves the grafts by the freeze-dried method. A card is filled out to accompany each graft. With this card the characteristics of the donor can be matched with those of the patient and a graft of suitable size selected.

An aortogram taken three months after the insertion of such a graft following resection of an aneurysm of the abdominal aorta showed that the graft was well filled with dye, was of normal calibre and was delivering a good flow of blood to the lower extremities.

Dr. Crystal and his co-workers have outlined the criteria for obtaining a successful graft. I would like to re-emphasize them: first, there must be a good inflow and outflow of blood. The graft must be of the same diameter as the artery of the host. If emobli are to be prevented, the artery must be occluded distally early in the operation and heparin should be injected into the graft during its placement to prevent thrombosis.

It is important that there be moderate tension at the suture line so that there is no kinking of the graft when the clamps are released.

J. Karl Poppe (Portland, Ore.): I would like to ask Dr. Crystal what criteria or methods he uses in determining the adequacy of the peripheral circulation beyond the stenotic or partially stenotic area?

Dean K. Crystal (closing): In answer to Dr. Poppe's question, we have been faced with the difficulty of adequate arteriography in our hospitals along with the problems of acquiring grafts and of judicious selection of patients. I have been reluctant even to try to convince skeptical hospital directors that we should buy expensive x-ray equipment. For that reason, we have used largely home-made materials, but we have come to the conclusion, at least in patients of fifty or fifty-five, that we should supplement aortography with peripheral arteriography as, for example, in the femoral vessel.

In addition, I am ashamed to say I denied my own physical senses as a clinical diagnostician in the patient in whom we had a failure. I felt the femoral pulses; and although the aortogram was good, I felt a thrill below both inguinal ligaments which should have indicated that his femoral vessels were too narrow.

Excisional Treatment of Arterial Deformities

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DURING the past decade arterial deformities, which heretofore were thought unamenable to corrective surgical procedures, have been treated with gratifying success by curative operations. The use of homologous arterial grafts and the development of tubes from plastic materials for re-establishment of continuity have made possible the excision of the deformity which otherwise could not be removed with restoration of normal hemodynamics. Homologous grafts were first used in this country by Gross[1] to replace defects in long coarctations of the aorta, the ends of which could not be united primarily. Subsequent use by Lam,[2] Dubois,[3] DeBakey and associates,[4,5] and others has further demonstrated the efficaciousness of arterial homografts for substitution of aneurysms and obliterative arterial disease. More recently, the development of synthetic fabric segments by Vorhees and Blakemore,[6] Hufnagel,[7] Shumaker[8] and others has opened up greater opportunities and virtually unlimited versatility for the replacement for these deformities.

AORTIC ANEURYSMS

Aneurysms may occur anywhere in the aorta and are due primarily to syphilis or arteriosclerosis, although traumatic aneurysms make up a relatively small number. Syphilitic aneurysms are seen much less frequently than previously due to more effective methods of treating syphilis. They usually occur above the diaphragm, often in the ascending aorta, are more apt to be sacular and are seen in relatively younger people. They may produce severe pain, frequently erode bone and are apt to obstruct the respiratory passages. The prognosis of intrathoracic aneurysms is poor. Kampmeier[9] reported 633 patients with this disease; only eighteen lived longer than two years after the onset of symptoms and most of them died within the first nine months. Zech and Merendino[10] found that of fifty patients with syphilitic aneurysms, eight died as a result of the aneurysm and thirty of the remaining forty-two died from complications directly related to syphilis, usually aortic insufficiency. All of these patients died within thirty-seven months after the onset of symptoms.

The surgical treatment of intrathoracic aneurysms poses a difficult problem because they are relatively inaccessible especially if they are in the ascending aorta or arch of the aorta, and because occlusion of the thoracic aorta is not usually tolerated for longer than twenty-five to thirty minutes. Spinal cord damage may occur if the period of occlusion is more than twenty to thirty minutes and in the older patient, who may already have hypertension, aortic valve disease, or disease of the coronary arteries, heart failure is more likely to develop during the period of occlusion. Lam and Aram,[2] who first reported the treatment of an intrathoracic aneurysm utilizing an homologous aortic graft, found that temporary partial paraplegia developed in their patient even though the circulation was arrested only twenty-four minutes on one occasion and fifteen minutes on another. On the other hand, DeBakey and Cooley[11] were able to occlude the thoracic aorta for forty-five consecutive minutes without evidence of damage to the spinal cord. Thus, it would appear that collateral circulation develops in some patients who have aneurysms. Hypothermia has been used successfully to lower the metabolic requirements of the central nervous system tissue

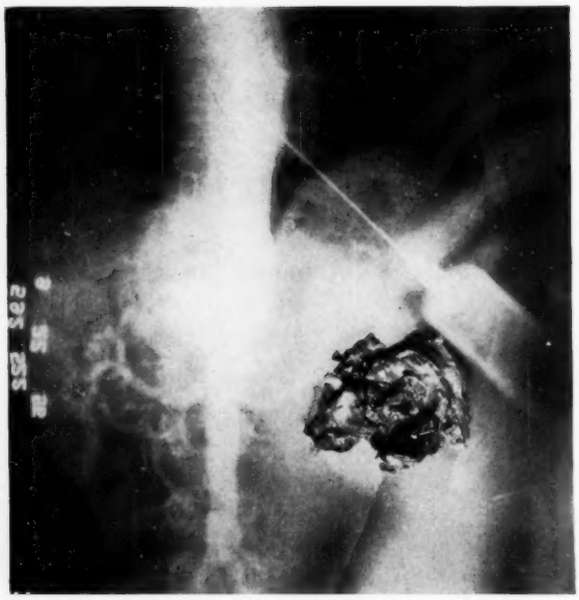


FIG. 1A. Aortagram demonstrating aneurysm located in crura of diaphragm. The aneurysmal sac proved to be larger than indicated by the opacity.

FIG. 1B. Photograph at operation showing tangential closure of aorta after aneurysm was excised.

so that occlusion of the thoracic aorta might be achieved for much longer periods of time.

We have operated upon four patients with intrathoracic syphilitic aneurysms. One, in a sixty-three year old man, involved the entire aortic arch and had become so large that it was producing pressure necrosis in the skin of the right supraclavicular fossa. Prior to exploration, it was thought to be an aneurysm of the innominate artery. However, operation revealed that it involved virtually the entire superior portion of the arch of the aorta. The right subclavian and carotid arteries were thrombosed. Clamps were placed along its junction with the aorta and the mass was excised. The left subclavian artery was anastomosed to the distal end of the left carotid artery over a polyethylene tube because the latter vessel arose from the aneurysmal sac. The patient's postoperative course was satisfactory and he was ambulated on the third postoperative day. However, approximately five days after operation he suddenly became restless and hemiplegia developed; he became progressively lethargic and comatose and died on the tenth postoperative day. In the second patient, a fifty-seven year old white man, the aneurysm (also in the arch of the aorta) was producing obstruction to the trachea and left main stem bronchus. The aneurysm was resected under hypothermia and an orlon fabric prosthesis was inserted to re-establish continuity. Cardiac arrest developed as the distal anastomosis was being performed but contractions were reinitiated and the anastomosis rapidly completed. He survived for approximately three hours postoperatively. In two other patients aneurysms of the descending aorta were excised tangentially with closure of the defect remaining in the aorta. (Fig. 1.) Both of these patients made a satisfactory recovery and have subsequently been asymptomatic.

Most abdominal aneurysms are the result of arteriosclerosis and fortunately occur below the renal arteries. They are usually fusiform and are not associated with severe pain except during the period of rapid enlargement or impending rupture. The prognosis is somewhat better than for syphilitic intrathoracic aneurysms. Estes[12] reported 102 cases; and of thirty-seven patients who could be traced, seven were found to have survived for a period of five years. Scott[13] reported that 70 per cent of ninety-six patients died within thirty-six months after the diagnosis had been made, and 17 per cent survived for five years. Zech and Merendino[10] found that twenty of forty-eight patients, or 42 per cent, with clinically diagnosed arteriosclerotic aneurysms died from rupture. All but one of their patients died within thirty-seven months after the diagnosis.

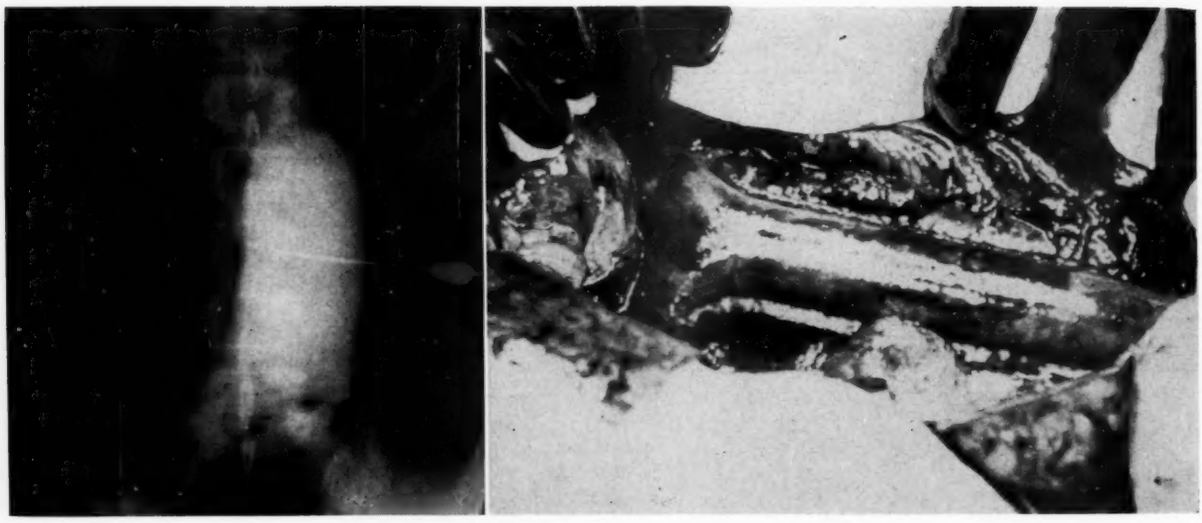
TABLE 1
ABDOMINAL AORTIC ANEURYSMS

Age (yr.), Race and Sex	Etiology	Location of Aneurysm	Procedure	Result
63, W, M	Arteriosclerosis	Aorta	Resection and homograft	Excellent
54, W, M	Arteriosclerosis	Aorta	Resection above bifurcation and homograft	Excellent
57, W, M	Arteriosclerosis	Aorta, ruptured	Resection and homograft	Excellent
55, W, M	Arteriosclerosis	Aorta	Resection and homograft	Excellent
61, W, F	Arteriosclerosis	Aorta	Tangential excision of aorta	Excellent
57, W, M	Arteriosclerosis	Aorta	Resection; orlon prosthesis	Excellent
46, W, M	Arteriosclerosis	Aorta	Resection; orlon prosthesis	Excellent
80, W, M	Arteriosclerosis	Left hypogastric artery, ruptured	Resection; primary anastomosis, left common iliac to left common femoral	Excellent
65, N, M	Arteriosclerosis	Aorta	Resection and homograft	Died 1 mo. postoperatively from acute myocardial infarct
68, W, M	Arteriosclerosis	Aorta, ruptured	Resection; orlon prosthesis	Good; absent left pedal pulses
54, W, M	Arteriosclerosis	Aorta	Resection; orlon prosthesis	Died 10 days postoperatively in uremia with acceleration of nephrosclerosis
72, W, F	Arteriosclerosis	Aorta	Resection above bifurcation; orlon prosthesis	Too early for evaluation

These figures emphasize the necessity for a vigorous curative approach in the treatment of intra-abdominal aortic aneurysms.

Abdominal aneurysms do not present problems of such great magnitude as those in the chest. The abdominal aorta can be clamped below the renal arteries for long periods of time without the development of spinal cord changes. When the aneurysm seems unusually high in the abdomen, aortography may be helpful in determining whether or not it lies below the renal arteries. Even though the aneurysm may seem high by external palpation, it will usually be located below these structures. Aortography is not routinely used to confirm the diagnosis of aneurysm because in most instances the diagnosis is obvious. It is particularly helpful in elderly individuals to differentiate a relatively small aneurysm from only tortuosity of the abdominal aorta. In approximately 40 per cent of our patients it has not given a true picture of the size of the aneurysm because of the presence of extensive thrombus in the aneurysmal sac.

Previous reports of DeBakey and Cooley,[11] and Bahnson[14] have excellently outlined the technical details of the procedure. The exploration is carried out through a midline incision which should extend virtually from the symphysis to the xiphoid process. The peritoneum is incised to the left of the mesenteric root, taking care not to injure the duodenum. The left renal vein crossing the aorta just above the duodenum can easily be injured if it is not carefully dissected free. It is helpful to clamp the aorta above the aneurysm and thus reduce the pressure during the remainder of the dissection. This maneuver facilitates the dissection from the surrounding structures with much greater ease. Ten cubic centimeters of a



2A 2B

FIG. 2. A, aortagram showing large abdominal aneurysm below renal arteries. B, operative view after aneurysm had been excised and orlon fabric prosthesis inserted.

solution of 1 mg. of heparin per cc. is injected into the aneurysm after it is clamped to prevent thrombosis. Care should be used in dissecting the aneurysm from the vena cava and iliac veins. If dissection is too difficult, a narrow strip of the aneurysmal sac can be left attached to the vena cava. The aneurysm is excised and the continuity is re-established by means of homograft or a plastic fabric tube. At present, we prefer an orlon fabric prosthesis because it is readily available and can easily be fashioned to fit the vessels to which it is anastomosed. In addition, experimental and clinical evidence shows that a fibrous tube develops to support it over a period of time. The great majority of intra-abdominal aneurysms should be resected because of: (1) their poor prognosis if untreated, (2) the rapid strides made in the development of technics for excision, and (3) the benefit achieved following operation. The very elderly patient with a small- to moderate-sized aneurysm which is asymptomatic and which has not been observed to increase in size over a period of several months or a year presents the greatest difficulty in deciding whether or not an aneurysm should be excised. Such a patient may have hypertension, generalized arteriosclerosis and impaired renal function, all of which may present a greater operative risk than if allowed to go untreated. Ideally, such a patient should be observed over a period of time to determine whether or not the aneurysm is enlarging, and operation should not be recommended in the very poor risk patient. On the other hand, if the aneurysm is enlarging rapidly or if rupture seems to be imminent, one has no alternative.

We have operated on twelve patients with intra-abdominal aneurysms from forty-six to eighty years of age, all of whom had aortic aneurysms except one who had an aneurysm involving the hypogastric and iliac arteries on the left. (Table 1.) Homografts were used in seven and orlon prostheses in three to re-establish continuity. (Figs. 2 and 3.) The hypogastric aneurysm was completely excised and a small sacular aortic aneurysm was excised tangentially and the aortic wall closed. Two deaths occurred in this series of patients, one approximately one month postoperatively from an acute myocardial infarction, and another one week postoperatively from progressive renal failure. The remainder recovered and have had satisfactory results. Three of the aneurysms, including the hypogastric artery aneurysm, were ruptured at the time of operation. All of these patients survived.

DISSECTING ANEURYSMS

Dissecting aneurysms constitute one of the most lethal forms of vascular disease. Because the dissection is often extensive, this deformity presents an entirely different problem from the treatment of fusiform and sacular aneurysms. In the vast majority of patients, the dissection begins in the intrapericardial

portion of the ascending aorta. It may then continue for a considerable distance and may pass down into the iliac and the femoral arteries. It may rupture through the adventitia or through the intima back into the aortic lumen. If the dissection extends into the femoral or iliac arteries, the intima may be so compressed that occlusion occurs and the patient will present typical symptoms of acute arterial insufficiency to the lower part of the body. If it ruptures through the adventitia, a large hematoma may result and tamponade may finally occur so that the bleeding stops; or rupture into one of the body cavities can occur and the patient will rapidly become exsanguinated. If it ruptures through the intima into the aortic lumen, a spontaneous cure occurs and patients have lived for a considerable period of time after the dissection. The acute dissection which begins shortly beyond the aortic valve not infrequently ruptures into the pericardium, often producing immediate death or severe pericardial tamponade with vascular collapse and shock.

The diagnosis is made primarily upon the clinical history and physical findings. There is often a history of hypertension and an initial sudden onset of severe pain in the back of chest which may radiate inferiorly. Loss of consciousness and shock may be present, especially if there is intrapericardial rupture. Symptoms related to the central nervous system often occur because the blood supply to the brain has been impaired by the dissection. Electrocardiographic examination may aid in ruling in or out a myocardial infarction, but DeBakey has pointed out that the presence of the electrocardiographic pattern of acute coronary occlusion does not exclude a dissecting aneurysm. An x-ray of the chest may show widening in the region of the aortic arch or descending aorta, especially if there has been considerable seepage of the blood into the mediastinal tissues. Aortography may be helpful in demonstrating a double or laminated opacity in the descending aorta when the diagnosis is in question.

We have recently operated upon four patients who were thought to have dissecting aneurysms of the aorta. Two with pericardial tamponade were operated upon within a few hours after the onset of symptoms. Active bleeding occurred in a fifty-seven year old man after the pericardium was entered, but was

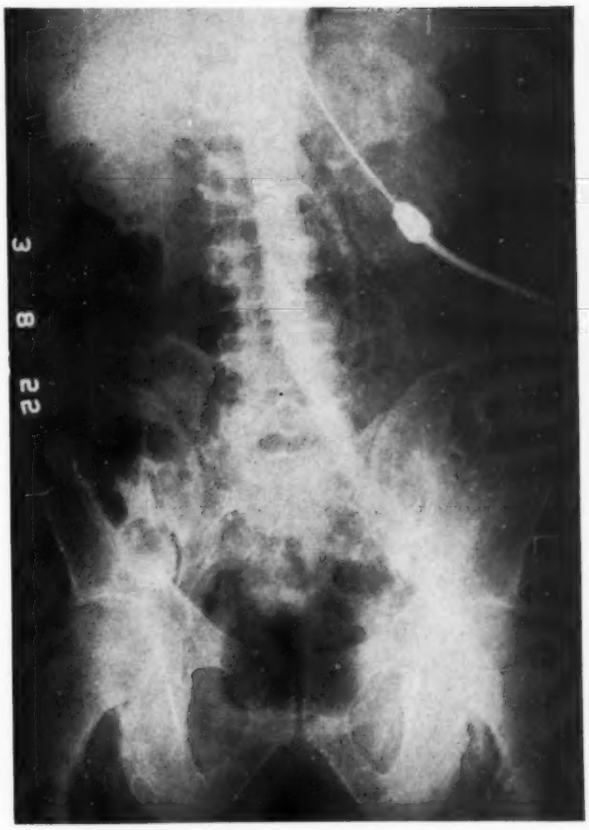


FIG. 3A. Aortagram gives no indication that thrombosed aneurysm is present. There is occlusion of the arteries on the right beyond the bifurcation.

controlled by suturing a band of orlon fabric around the intrapericardial portion of the aorta. This patient died approximately fifteen days later from myocardial infarction. At postmortem examination a rupture could not be demonstrated in the intima or adventitia of the ascending aorta.

A comparable procedure was performed in a similar patient, a 52 year old man, who died three days postoperatively and was found to have a circumferential rupture of the intima approximately 2 cm. distal to the aortic valve. The entire intima had invaginated through the lumen of the aorta causing partial obstruction not only to the aorta but also to the vessels arising from the aortic arch. In another patient, a fifty-six year old woman, the diagnosis was confirmed by aortography. Twenty days after the dissection occurred, the procedure advocated by DeBakey, Cooley and Creech[15] was performed. This consists of dividing the thoracic aorta, closing the layers of the lower end and fashioning an intimal window in the upper segment, and reanastomosing the aorta.

FIG. 3B. Operative exposure showing large thrombosed aneurysm at bifurcation.

FIG. 3C. An homologous homograft insertion after the aneurysm was excised.

This patient has done satisfactorily since operation and is asymptomatic.

Sudden dissection occurred in a forty-nine year old man with severe hypertension. It began just below the left subclavian artery and extended inferiorly, resulting in occlusion of the iliac arteries and paraplegia. Abdominal exploration was performed and it was necessary to resect the bifurcation of the aorta and insert an orlon fabric graft in order to re-establish continuity. A window was fashioned in the intima of the superior segment of the aorta. This patient regained full use of his lower extremities but died from renal failure approximately one week postoperatively. These cases will be reported in more detail subsequently.

OBLITERATIVE DISEASE OF THE AORTA

Leriche first described the syndrome which bears his name in 1923,[16] and called attention to it again in 1940[17] and 1948.[18] This syndrome is manifested by progressive symptoms of arterial insufficiency involving the entire lower extremities. It usually begins with intermittent claudication which often progresses to involve the thighs and the buttocks. Not infrequently the patient's chief complaint is pain in the lower part of the back and hips. Coldness and numbness is present in the legs and feet. Incapacity is so severe that these patients can walk only short distances without becoming extremely fatigued in the lower extremities. Another frequent symptom is sexual impotence.

Pathologically the disease consists of extensive atheromatous infiltration of the major arteries with progressive central thrombosis up the abdominal aorta. These changes appear to be most marked in the iliac arteries; and when these vessels become occluded, thrombosis occurs and progresses upward to the level of the renal arteries, occasionally continuing to occlude the renal arteries. A direct operation on the aorta is advised because of the incapacitating nature of the disease and the tendency for progressive cephalad thrombosis of the aorta to occur. Lumbar sympathectomy has been performed but is a palliative procedure and yields only temporary benefit.

In 1947 dos Santos[19] performed the first direct procedure, a thromboendarterectomy, in which the intimal layer containing the atheromatous and thrombotic material was removed, leaving the adventitia to serve as a conduit for blood flow. Wylie,[20] and Cannon and Barker[21] have used this procedure successfully while others have abandoned it because of the high rate of failure. Rob,[22] Julian and associates,[23] and DeBakey and associates[24] have advocated resection of the thrombotic aortic bifurcation with insertion of a homologous arterial graft to re-establish continuity. Rob uses thromboendarterectomy when the disease is localized and minimal. When resection of the aortic bifurcation is performed, it is necessary to employ thromboendarterectomy on the distal iliac and hypogastric arteries in most instances and also on

TABLE II
LERICHE SYNDROME

Age (yr.), Race and Sex	Degree of Occlusion	Location of Occlusion	Procedure	Result
65, W, F	Incomplete	Aorta, both iliac arteries	Resection of bifurcation, iliac arteries; homograft; distal thromboendarterectomy	Excellent
55, W, M	Complete	Aorta at renal arteries	Resection of bifurcation, iliac arteries; homograft; distal thromboendarterectomy	Excellent
65, W, M	Complete	Aorta	Resection of bifurcation, iliac arteries; orlon prosthesis; distal thromboendarterectomy	Excellent
54, W, M	Incomplete	Aorta, left common iliac artery	Thromboendarterectomy, aorta, left common iliac and left femoral arteries	Excellent
47, W, M	Incomplete	Aorta, both iliac arteries	Thromboendarterectomy, aorta and both common iliac arteries	Excellent
64, W, M	Complete	Aorta	Resection of bifurcation; orlon prosthesis; distal thromboendarterectomy	Excellent
52, W, M	Complete	Aorta	Resection of bifurcation; orlon prosthesis; distal thromboendarterectomy	Excellent
57, W, M	Complete	Right common iliac artery	Thromboendarterectomy, right common iliac artery	Excellent
53, W, M	Complete	Aorta	Resection of bifurcation; orlon prosthesis; distal thromboendarterectomy	Excellent
61, W, M	Incomplete	Aorta and right iliac artery	Thromboendarterectomy, lower aorta; right iliac and femoral arteries to popliteal artery; left iliac and femoral arteries	Excellent

the superior segment of the aorta in order to achieve adequate lumens.

Ten patients with aortic obliterative disease were operated upon in this series. (Table II.) All but one were male, and their ages ranged from forty-seven to sixty-five years. Six had complete and four had incomplete occlusive changes. Four with complete occlusion had absent pulses below the inguinal region, as did two of those with incomplete occlusion. The remainder had markedly diminished pulses in the feet and ankles. The diagnosis was confirmed by aortography in all but one patient who was sensitive to the contrast media. Resection and grafting were performed on all patients with complete occlusion and on one of the patients with partial occlusion. In four with partial occlusion the involved area was not extensive and was successfully treated with thromboendarterectomy. In the six remaining patients resection of the bifurcation was performed utilizing homologous arterial grafts in two and orlon fabric prosthetic tubes in four. (Fig. 4.) All of the patients survived and had a return of dorsalis pedis and posterior tibial pulsations with relief of intermittent claudication and pain in the back and hip.

The major question arising in the management of patients with this problem is whether or not obliterative changes will recur in these arteries or in the inserted grafts. Since this is often one manifestation of a generalized disease, it seems entirely likely that it might. On the other hand, patients on whom others have performed similar procedures are alive and apparently free of recurrence as long as three years after operation. Another question which arises is whether or not one should use an arterial homograft or a plastic prosthetic tube. Although the homograft is technically easier to use, the recent work of Creech and associates[25] indicates that atheromatous deposits are less

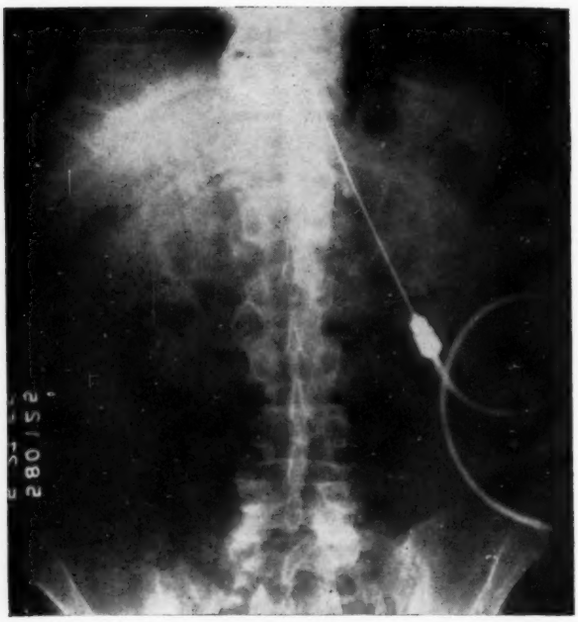


FIG. 4A. Aortagram showing complete occlusion of abdominal aorta.

FIG. 4B. The obliterated aorta was resected and an orlon fabric prosthesis was inserted.

likely to occur when the plastic materials are used. Thromboendarterectomy seems entirely satisfactory in experienced hands, but an excisional procedure utilizing a graft appears to be generally preferred.

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DISCUSSION

Herbert J. Movius (Long Beach, Calif.): It is my belief that a discusser should present differences in opinion, relate pertinent personal experiences and emphasize worthy points.

Our experience with excision of thoracic aneurysms is unusual in that it is limited to four patients each with traumatic aneurysms. Three of these aneurysms were very similar, arising just beyond the left subclavian artery, measuring about 8 cm. in diameter. All patients were asymptomatic except for one who had vague pain and hoarseness. Each aneurysm had occurred sometime after fairly severe, non-penetrating trauma to the chest.

The course of untreated asymptomatic arteriosclerotic aneurysms is not proved despite many reports concluding the prognosis is grave. The patients with symptoms or the relatively young good risk patients do not present a problem in selection. At the Long Beach Veterans Hospital we still do not resect asymptomatic aneurysms in the elderly or poor risk patients.

We agree that aortography is not usually needed either for diagnosis or for planning the procedure. A lateral roentgenogram of the abdomen will usually confirm the diagnosis of aneurysm.

The technical problem of making a satisfactory anastomosis between arteries in which there is considerable discrepancy in size has been greatly facilitated by suturing a small segment of ascending aorta to the host aorta and then anastomosing this to the bifurcation graft. This has an additional advantage in that it allows the surgeon to make his lower anastomoses on a tension-free, maneuverable graft, and the graft-to-graft anastomosis, which is very easy, can be made last.

In the only patient with ruptured aneurysm we have operated upon, the thorax had to be opened in order to control hemorrhage by finger compression of the thoracic aorta. In this patient the procedure was life-saving. Therefore, it is suggested that patients with bleeding aneurysms be draped so that the thorax may be quickly and aseptically entered, if not actually opened before dissection about the aneurysm is begun.

Another suggestion is to always drape the patient with both femoral areas exposed. The femoral pulses should be palpable before the operation is considered finished. This draping allows the surgeon to extend the graft easily to either femoral artery if necessary, a procedure we have had to perform in three of thirty-one patients, and should have carried out in two others.

Leriche's syndrome is far from a rare entity. It is seen rather commonly in the younger age groups. Twelve of sixty-seven such patients we have seen were under the age of forty. The youngest was twenty-eight and had been having severe symptoms for three years.

We have performed endarterectomy upon the majority of patients, and have been very well satisfied with the procedure when the involvement remained above the bifurcation of the common iliac arteries. Twenty-seven of twenty-eight patients had excellent results. The remaining patient died from thrombosis of the superior mesenteric artery on the twelfth postoperative day.

The critical point in endarterectomy is the distal end, and the most perplexing problem is where to stop. Neither of these are solved by excision and grafting.

Endarterectomy is contraindicated in (1) a very narrow artery, (2) an artery with a segment or two that is narrowed, and (3) in patients who have had previous unsuccessful direct arterial surgery.

William H. Muller, Jr. (closing): We would certainly agree that all arteriosclerotic aneurysms of the abdominal aorta should not be resected, particularly in the elderly patient when the aneurysm is not large, and especially when one has an opportunity to follow the patient for a period of time.

I think Dr. Movius' method of controlling the bleeding in the patient who has a ruptured abdominal aorta by entering the chest is an excellent suggestion. We have controlled bleeding in these patients by having the assistant compress the aorta with his hand through the abdominal incision. The surgeon can then quickly mobilize the aorta above the aneurysm and place a clamp across it.

It will take a longer period of time to determine whether endarterectomy or replacement procedures will evolve as the best treatment for ob-

literative disease. I believe that one reason many people have had difficulty in achieving good results with endarterectomy is because the intimal plaques with the thrombotic core do not separate in one plane but probably several planes in the media, and there are shreds and tags of the media which often will remain, especially in the smaller vessels. Thrombus formation may occur about these tags, thus causing the endarterectomized area to thrombose. This happened in one of our patients and it was necessary to re-explore and evacuate the artery to re-establish blood flow. The administration of heparin for twelve to twenty-four hours postoperatively in small to moderate doses is helpful in maintaining patency following endarterectomy.

Abdominal Wound Disruption with Eventration

REPORT OF FORTY CASES

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BECAUSE all forms of abdominal incisions (no matter how skillfully fashioned) weaken the integrity of the abdominal wall, abdominal wound disruption continues to remain a disconcerting complication, apt to plague any abdominal surgeon at one time or another. No one who is called upon to operate within the abdominal cavity frequently can flatter himself with anything like reasonable assurance that he will forever escape this disaster. Most of us fervently hope to have limited personal experience with wound disruptions, and to this end it behooves us to reconsider periodically all possible factors involved in their occurrence.

The persistent concern of surgeons over this problem is reflected in the frequent appearance of articles on the subject during the past fifty odd years. However, despite the considerable elucidation of factors involved in wound healing,[1,57,58] improvements in surgical technic[17,37,41,56] and a better understanding of the physiologic principles related to the pre- and postoperative care of the surgical patient,[12,29,31,52] we have not significantly altered the incidence and the mortality rate of this serious and sometimes catastrophic complication of abdominal surgery.[13,30,49,61]

Many synonyms have been employed in identifying this disorder, such as: evisceration, wound dehiscence, avulsion, burst-wound, wound separation and wound disruption. The colorful term, burst-wound, is popular in England. In America perhaps the most commonly employed term in hospital parlance is evisceration. We have preferred to avoid this term since it means to disembowel or to tear out the viscera. Although such a term might accurately describe something done by the pathologist or by an experimental worker, it seems a mite too spectacular a description to employ in identifying the postoperative complication at hand.

We have preferred to identify this complication by the term wound disruption with eventration or, in other words, a wound separation of such magnitude that abodminal viscera (usually intestinal coils) are either visualized in the wound or have prolapsed onto the abdominal wall.

Incidence. Even a cursory review of the incidence rate of wound disruption immediately impresses one with its probable underestimation in most reports. The vagaries of samplings (such as this study entails) reflect the shortcomings of most data obtained from record-room files.[13,15,55] We do not offer our incidence rate as in any conceivable way accurate, and agree quite completely with Whipple[55] that the only way an accurate percentage can be obtained is from a predetermined program set up for actual studies of laparotomy cases followed by wound disruption during a certain period of time.

This complication is altogether too frequently omitted from the diagnostic files, especially in those cases in which no secondary closure is performed. It is impossible to be certain that one has included all of the cases handled by taping and tamponade in the privacy of the patient's room. The physician may neglect to record the reason for "taping" or fail to recognize the less spectacular case as being indeed a disruption with eventration. Nurses' notes often help identify such situa-

TABLE 1

INCIDENCE AND MORTALITY RATE IN VARIOUS REPORTED SERIES

Year	Author	Laparotomies	No. of Cases	Incidence (%)	Deaths	Mortality (%)
1932	Sokolov	.....	723	2–3	226	34
1934	Colp	2,750	24	0.9	7	28
1936	Glasser	3,234	8	0.24	5	63
1946	Joergenson and Smith	39,474	97	0.24	42	43.8
1949	Wolff	1,700	45	2.6	7	11.1
1953	Del Junco and Lange (present series)	11,334	40	0.35	7	17.5

tions, but of course cannot (and should not) be expected to be entirely reliable.

Some incidence rates are considerably reduced by including all herniorrhaphies.

In our analysis of 11,334 laparotomies (excluding herniorrhaphies) performed on the surgical service at the Queen of Angels Hospital in Los Angeles, California, during the period from January 1, 1948, through December 31, 1952, we found an incidence of 0.35 per cent.

Comparable figures of the incidence rate during the past two decades are illustrated in Table 1. It will be observed that Wolff[61] reports an incidence of 2.6 per cent—a rate considerably higher than that reported by other investigators.[5,9,24,30,49] We believe that because of the careful recording and analysis of Wolff's study, the incidence reported by him reflects more accurately the probable incidence rate and at the same time gives the reader a reasonable impression of the inaccuracy of our own figures.

In attempting to assess the effect of wound disruption upon mortality, one again must despair of any reasonable accuracy.

Some authors[14] have made estimates that perhaps one-third to one-half of the deaths occurring shortly after this disastrous complication could be ascribed to it.

No one can speak with certainty on this matter since many of these patients are desperately ill to begin with, are often afflicted with a multiplicity of disabling disorders, and an operation of considerable magnitude is attempted out of sheer necessity. A subsequent wound disruption, while it may be a contributory factor, is only one more incident to be endured before what would have been a fatal outcome without this added affliction.

Colp[6] believes that wound disruption itself is fairly innocuous and contributes very little to the fatal outcome. Sokolov,[49] in a collective review of over 700 cases obtained by questionnaires directed to European surgeons, reported a mortality rate of over 30 per cent. Later studies in this country by Colp,[6] Jenkins,[22] Glasser[9] and others[13,32] report a mortality rate varying from 11.1 to 63 per cent. Moreover, the more recently reported series[24,61] fail to indicate any significant lowering of the mortality rate in this situation. Most major studies encountered in the literature, however, do not make any attempt to evaluate the relative "blame" or responsibility of such factors as the patients' general condition, underlying disease or primary operation.[13,22,49]

In our own series the mortality rate was 17.5 per cent. We have tried to the best of our ability to evaluate the degree of responsibility for those deaths attributable directly to wound disruption, and have concluded that in all but one instance (six of seven deaths) wound disruption was indeed the cause of death. It also occurred to us that some "explanation" for our relatively low mortality is reflected in the fact that these wound disruptions did not occur in as seriously ill patients as were represented in comparable series. Nevertheless, even this mortality rate is disconcertingly high and emphasizes the seriousness of such a complication (for which the average mortality of reported cases approximates 35 per cent).

We were encouraged to note that in at least one report some improvement has been observed. Mayo and Lee[30] report a drop in mortality from 34.6 per cent for the period 1925 through 1929 to 18.1 per cent for the period covering 1945 through 1949. It was of particular interest to us to see that they report no

deaths in the few cases with anatomic incisions (oblique and transverse).

ETIOLOGY

No single factors can account for all wound disruptions. Most occurrences would appear to be the result of a combination of unfavorable influences. Occasional instances have been described where the causative background remained obscure.

The basic factors (general and local) concerned in wound healing have been thoroughly discussed in many excellent papers.[13,22,35,49] Indeed, both the clinical and experimental background of these influences are so well documented in most standard texts on surgery or pathology that there is no reason for considering them at length in this review.

Suffice it to say that for our immediate purpose we are more concerned with the factors tending to prolong the lag period or "quiescent" phase of wound healing. At present, at least, little can be done about accelerating this phase. It is during this phase that approximation must depend upon the suture material entirely since the wound possesses no tensile strength of its own.

A more detailed discussion of the factors in the general problem of wound healing which bear upon wound disruption is worth while. We have grouped these into major and contributory factors, as we interpret them.

Major Factors. The majority of writers on the subject emphasize the major or immediate causes of wound disruption as generally associated with marked increases in intra-abdominal pressure or severe muscular strains, with severe infection occasionally playing the significant role.

Certainly wounds which disrupt before the fifth day can hardly be blamed on faulty wound healing.

Marked Increases in Intra-abdominal Pressure. Marked increases in intra-abdominal pressure are occasioned by such acts as coughing, retching or vomiting, sneezing, singultus and straining at the stool or urination. Abdominal distention probably plays a more passive or contributory role to all the preceding factors, and obesity is involved in a similar manner.

In going over our cases (Table II) it was quite apparent that wound disruption occurred most frequently in those patients who had a "stormy," prolonged postoperative course associated with factors responsible for marked increase in intra-abdominal pressure. Similar observations have been frequently recorded.[9,27,31,46,53,61] Indeed, it is rare to observe wound disruption complicating an apparently uneventful post-operative course, although it has been said to occur.[54]

TABLE II
MAIN CAUSES OF WOUND DISRUPTION

Causes	No. of Cases	Per cent
I. Increased intraperitoneal pressure due to:		
Atelectasis	15	36.6
Abdominal distention	9	21.9
Atelectasis plus abdominal distention	8	19.6
Pneumonia	2	4.8
Asthma	1	2.4
II. Infection	6	14.7

It will be noted that for the most part the acts responsible for significant increases in intra-abdominal pressure are reflex or involuntary ones which produce sudden or explosive changes, rather than the type of change brought about by a voluntary or controlled act such as ambulation.

Murphy and Mengert[34] in 1933 investigated the changes in intra-abdominal pressure produced by voluntary muscular effort as measured by a distended balloon placed in the vagina. They observed much higher levels during sharp abdominal contractions than those produced by slow and progressive muscular contraction.

Somewhat later Glasser,[9] Melbert[31] and others,[23,46] in reporting small series of wound disruptions, emphasized the primary etiologic role of increased intra-abdominal pressure in wound disruption.

More recently, Drye[8] carried out ingenious measurements of intra-abdominal pressure changes in patients undergoing abdominal operations. These measurements were effected by placing a rubber condom, tied over the end of a urethral catheter, into the peritoneal cavity and bringing the catheter out through a stab wound and attaching it to a water manometer. Drye was able to demonstrate by these

observations that during involuntary acts such as vomiting or coughing, pressure levels of 80 to 150 cm. of water were attained—levels several times those observed during voluntary acts such as getting out of bed and walking (29 and 18 cm. of water).

It would be interesting to obtain similar studies in certain patients we have all observed from time to time—patients who, for want of a better term, might be referred to as "specialists at coughing." We refer to obese, emphysematous, brachymorphic males of massive musculature afflicted with a chronic cough. Over the years they must certainly develop a talent for increasing intra-abdominal pressure that would probably require a mercury manometer to make measurement a practical problem.

Price[37] has demonstrated that in abdominal incisions the greater the intra-abdominal pressure, the greater the tension upon both the entire suture line and individual sutures.

Wolff,[61] in an excellent exposition of this problem, cites two instances of wound disruption occurring as a result of tracheal stimulation during tracheobronchial tree toilet at the conclusion of the operation. In these instances there was no question of wound healing or holding power of tissues. The sutures simply broke as the result of powerful mechanical forces occasioned by retching, straining and violent cough resulting from tracheal stimulation. We recently had the opportunity to observe a similar occurrence.

Landry et al.,[27] in reporting sixty-one cases of wound disruption, observed that coughing, abdominal distention or vomiting was a predominant finding in fifty-seven cases; in other words, in 95 per cent of those cases the intra-abdominal pressure changes were produced by one or more of the mechanisms cited. In five of their cases involving lower midline incisions, an additional mechanism (namely, urinary retention) contributed to the intra-abdominol pressure change.

Severe Muscular Strain. It is difficult for us to separate the role of severe muscular strain from the type of incision employed. Since it appears inescapable that whatever be the exciting cause of such strain, the effect of the resulting strain on the suture line will be significantly influenced by the efficiency with which this strain is applied to the suture line.

A consideration of the influence of severe muscular strain upon wound disruption is therefore essentially a consideration of the relative advantages and disadvantages of anatomic (oblique and transverse) and non-anatomic (vertical) incisions in relation to wound disruption.

The transverse incision has been employed by surgeons for over 100 years,[41] although it did not become popular until 1900 when Pfannenstiel[36] used it in pelvic operations.

Since then, of course, numerous references have appeared in the surgical literature citing the advantages of the transverse or oblique incision in abdominal surgery.[41,45–48] To those surgeons who employ it almost exclusively in abdominal surgery it seems incredible that so many excellent surgeons continue to prefer a vertical incision.

The important muscles of the abdominal wall are the "flat muscles" (external oblique, internal oblique and transversus abdominis). By virtue of their almost encircling the body they play a significant role in alteration of intra-abdominal pressure. They are never at rest since they are important respiratory muscles, relaxing as the diaphragm descends during inspiration and contracting during expiration, forcing the now relaxed diaphragm upward by increased intra-abdominal pressure produced by their contraction. During involuntary acts such as coughing, vomiting or sneezing the sudden pull of these muscles must be very considerable. Strong voluntary contraction of these muscles is required during defecation and to a lesser degree in most instances during micturition.

Since the fibers of these flat muscles run in a transverse (or oblique) direction, the abdominal fascial fibers (which are the tendinous continuations of these muscle fibers) likewise run in a transverse or oblique direction.

This fascia of the abdominal wall is of considerable importance to the surgeon since it affords him the only reliable "holding material" in effecting wound closure.

If these fascial fibers are cut transversely to their long axis, as they are by a vertical incision, it will require considerably greater effort to approximate them than it would if a transverse incision were employed since such an incision parallels the direction of these fibers.

Moreover, in approximating a vertical incision the sutures must parallel the strong

fascial fibers, whereas in the case of a transverse incision the approximating sutures pass across these fibers thereby making for a more secure closure.

The importance of muscular strain across suture lines has been well illustrated by Sloan.[47] By employing spring scales attached to forceps he was able to measure quantitatively the force required to approximate the edges of various types of incisions with the patient under light anesthesia. His most startling observations resulted from such investigations on L-shaped incisions (a combined vertical and transverse type of incision). He demonstrated that it requires a force thirty times greater to approximate the edges of the vertical segment as compared to the transverse segment.

Sloan also demonstrated that with vertical incisions the longer the incision, the greater the force required to bring the wound edges together—the force increasing in proportion to the square of the length of the incision (approximately 30 pounds pull for a 3 inch incision, 50 pounds for a 4 inch incision, and 80 pounds for a 5 inch incision).

Since practically no pull is required to approximate the edges of a transverse incision, the disadvantage of the vertical incision becomes quite apparent when one bears in mind that the forces measured by Sloan were observed under light anesthesia. Frightfully greater forces must be imagined during retching, coughing, sneezing or uncontrolled straining.

Singleton,[45,46] in his exhaustive survey of 9,000 consecutive abdominal incisions, could find only one wound disruption in 3,147 anatomic incisions, or an incidence of 0.031 per cent. Among the 5,853 non-anatomic or vertical incisions, he found sixty instances of wound disruptions, or an incidence of 1.02 per cent.

It is worth noting that if one compares these disruption rates, it is apparent that wound disruption occurred approximately thirty-three times more frequently in the vertical incisions. This number, thirty-three, is pretty close to the number that proved significant in Sloan's[47] observations when he noted that it took a force thirty times as great to approximate the vertical segment as compared to the transverse segment of an L-shaped incision.

We believe this similarity to be more than a strange coincidence, and it would take a great deal of mental gymnastics and even more eloquence to divert our focus from the very significant relationship between wound disruption and the type of incision employed.

Our own figures, although less spectacular than Singleton's reflect the same increased hazard of the vertical incision. (Table III.)

TABLE III
OPERATIVE INCISIONS

Incisions	Upper Abdomen			Lower Abdomen			Total	
	No.	%	Drain	No.	%	Drain	No.	%
Non-anatomic								
Midline	3	7.5	..	8	20	..	11	27.5
Paramedian	14	35	3	4	10	..	18	45
Right and left rectus	2	5	..	2	5	..	4	10
Thoracoabdominal	1	2.5	..	..	....	..	1	2.5
Anatomic								
Subcostal	1	2.5	..	..	....	..	1	2.5
Transverse	2	5	..	1	2.5	..	3	7.5
McBurney	..	....	..	1	2.5	..	1	2.5
Thoracoabdominal	1	2.5	..	..	....	..	1	2.5
Total	24	60	3	16	40	..	40	100

Considering cholecystectomy alone, it will be noted (Table IV) that 1,093 cholecystectomies were performed during this period; and even though the transverse incision was employed more frequently, only two wound disruptions occurred in this group as compared to five where the vertical incision was employed.

Most authors report a greater frequency of wound disruption in the upper abdomen than in the lower. Two-thirds of the disruptions in White's[59] series occurred in the upper abdomen. Landry et al.,[27] in confirming this observation, point out that this is inversely proportional to the ratio of these incisions in the unruptured cases.

Infection. The rate of infection in wound disruption is difficult to evaluate. Case record analysis is often unreliable on this score, since one is apt to find too little information to evaluate the severity of the infection and its time of occurrence.

It is reasonable to suppose that severe infection might cause wound disruption not only by its disintegrating effect on tissue and absorbable suture material but also by interference with wound healing.[18,32,56]

One cannot refrain from the observation that while the introduction of potent chemotherapeutic and antibiotic agents has done much to reduce the incidence of wound infection, it has not influenced the incidence of wound disruption noticeably. Moreover, only a very small percentage of infected wounds disrupt.

TABLE IV
INCIDENCE OF WOUND DISRUPTION IN CHOLECYSTECTOMIES FROM 1948 TO 1952

Incisions	No. of Cholecystectomies	%	No. of Wound Disruptions	%
Vertical.....	473	43	5	1.06
Transverse...	620	57	2	0.32

Significant wound infection was reported in six (15 per cent) of our forty wound disruptions. White[59] lists infection as seeming to be the chief cause of wound disruption in eight of his thirty cases.

CONTRIBUTORY FACTORS

Age. Wound disruption may occur at any age,[22] although it is probably true that its occurrence is observed more frequently in the older age groups.[13,61] It is doubtful that age alone has much to do with the matter, since the older age group is the one in which we can reasonably expect increased nutritional disorders, pulmonary complications and other afflictions of the aged.

In our series, 70 per cent of the disruptions occurred in patients over fifty years of age.

Sex. Most series report a preponderance of wound disruptions in males.[6,13,30] The ratio is generally estimated at approximately two males to one female.[13,32,49,61] The explanations for this sex difference are often more amusing than informative. However, it has been frequently observed that women seem to have a greater tolerance to withstand surgical procedures. Men, because of their greater muscular development and various physical factors, would appear to have a significantly greater hazard of wound disruption.[6,31] In our series of forty cases there were thirty-one males and nine females.

Constitutional Diseases. The role of diabetes, jaundice, emaciation, obesity, acute or chronic intoxication, syphilis, tuberculosis and other chronic disorders, has been amply bandied about without much uniformity of conclusions reached. Howes[19] has written a sound and succinct summary.

Constitutional diseases *per se* would appear to have little effect on wound healing, provided specific factors such as malnutrition, dehydration, anemia, hypoproteinemia or serious vitamin deficiencies are not present.[33]

Although anemia has been blamed for poor wound healing,[13,49] recent studies have inferred that even this factor has but little deleterious effect upon the healing process.[62]

In our series we were surprised to find how often the patients were described as in relatively good physical condition preoperatively. Only two patients were considered emaciated. Twelve were described as "overweight." If we consider hemoglobin of 11 gm. per cent level as an arbitrary critical level, 92.5 per cent of our cases were "within normal limits," so that anemia did not appear to be a significant factor.

All in all, we classified our patients preoperatively as excellent preoperative risks in 70 per cent, fair risks in 22.5 per cent and poor risks in 7.5 per cent.

It is our personal impression that of the constitutional factors, obesity and chronic cough offer the greatest threat with respect to wound disruption.

Primary Disease. As in the case of constitutional diseases, the exact importance of the primary disease in wound disruption is difficult to assess. Colp[6] regards the primary disease as the most important factor underlying the etiology of wound disruption. The role of cancer has been frequently emphasized in relation to wound disruption,[6,30] and it is true that carcinoma is reported as the primary disease in approximately 25 per cent of the cases. This should not be too surprising since it probably reflects a combination of factors bearing upon wound disruption.[61] These are the patients more likely to be in the older age group; they are likely to be malnourished since the malignancy more often than not involves one or another digestive organ. These are the patients most likely to undergo the longest, most extensive operations, and the ones most likely to have the postoperative complications which are most conducive to wound disruption.

In our series the most frequent primary disease associated with wound disruption was carcinoma. (Table v.) The most frequent site of carcinoma was the colon, a finding frequently noted in other reports.[23,30]

What interested us most from the standpoint of primary disease were the cases involving the gallbladder. Seven wound disruptions occurred in patients undergoing operation for uncomplicated cholecystitis with cholelithiasis. In every instance the disruption was associated with severe respiratory complications that were either inadequately or improperly treated. It was also surprising to find that six of the seven disruptions occurred in males (although females are operated upon for this conditions much more frequently). (Table vi.)

TABLE V
DIAGNOSIS

	No. of Cases	%
Carcinoma	13	32.5
Colon	8 (20%)	
Bladder	2 (5%)	
Stomach	1 (2.5%)	
Uterus	1 (2.5%)	
Ovary	1 (2.5%)	
Cholecystitis with cholelithiasis	7	17.5
Duodenal ulcer	8	20
Bleeding	2 (5%)	
Elective	6 (15%)	
Gastric ulcers	3	7.5
Perforated	1 (2.5%)	
Bleeding	1 (2.5%)	
Elective	1 (2.5%)	
Miscellaneous	9	22.5
Pregnancy (eclampsia)	1 (2.5%)	
Pyloric stenosis (baby)	1 (2.5%)	
Abdominal aneurysm	1 (2.5%)	
Cirrhosis	1 (2.5%)	
Volvulus (ileum)	1 (2.5%)	
Fibroma uteri	1 (2.5%)	
Appendiceal fibrosis	1 (2.5%)	
Laparotomy (hypermenorrhea)	1 (2.5%)	
Chronic salpingitis and leiomyoma	1 (2.5%)	

Duodenal and gastric diseases were also prominent in our series (Table v), as they have been in many other series.

Biochemical Changes. Both clinical and experimental investigations have demonstrated a definite relationship between wound healing and certain biochemical changes. Curiously enough, if one searches long enough, he can usually find any of the factors cited as either important or unimportant in the voluminous literature on these alterations.

It would seem reasonable to suppose that adequate proteins are necessary to have wound repair proceed apace, and that to restore protein deficiencies any existing anemia must be corrected.[39] Thompson and co-workers[50,51] have demonstrated that the wounds of hypoproteinemic animals disrupted frequently and that restoration of the serum protein levels with lyophilized plasma during the immediate postoperative period could avert this complication. Kobak and his co-workers[25] demonstrated a lag in tensile strength of wounds in hypoproteinemic animals, most apparent on the fifth day (three times as strong in control animals). However, thereafter the wound strength rises in parallel fashion, with the low protein group lagging by approximately two days.

The serum protein levels were investigated in only half of our forty cases; 75 per cent of these showed total serum protein levels above 6 gm. per 100 cc. of blood, and only one patient could be considered hypoproteinemic, so that hypoproteinemia did not appear to be a significant factor in this series. In Wolff's[61] series 62 per cent had low serum proteins and he regarded hypoproteinemia as probably rather significant.

A definite relationship between satisfactory wound healing and vitamin C has been accepted for many years. Experimentally and clinically, this relationship has been frequently investigated.[2,21,28,60] It is a demonstrable fact that humans on prolonged ascorbic acid depletion will exhibit retardation in the development of tensile strength in wounds apparently due to failure of fibroblastic proliferation and intercellular collagen production. It has even been observed that already formed collagen of apparently normally healed wounds may revert to precollagen if scurvy supervenes.

Low ascorbic levels appeared to be a significant factor in wound disruptions in the series reported by Hartzell et al.[14] but were of no significance in Wolff's series[61] (that series in which low serum proteins appeared significant).

In our series plasma ascorbic acid levels were not determined. However, it has been demonstrated that preoperative ascorbic levels are less important to wound healing than the postoperative levels attained. Adequate wound healing will occur despite low preoperative ascorbic acid levels if adequate ascorbic acid replacements are maintained during the postoperative period.[2] Since 80 per cent of our forty

TABLE VI
CHOLECYSTECTOMIES WITH WOUND DISRUPTION*

Case No.	Incision	Sutures	Technic	Retention Sutures	Nausea and Vomiting	Coughing	On Suction	Obesity
1244	V	Absorbable	Interrupted	o	..	x	o	x
10018	V	Absorbable	Interrupted	x	..	x	o	x
1917	V	Wire	Interrupted	x	..	x	x	..
2925	V	Absorbable	Continuous	x	..	x	x	x
10488	V	Cotton	Interrupted	o	..	x	x	..
12606	T	Silk	Interrupted	o	..	x	o	..
9707	T	Absorbable	Continuous	x	x	x	x	..

* Ages of patients, 52 to 68 years. Sex: male, 6; female, 1.

patients received daily doses of at least 500 mg. of ascorbic acid throughout the postoperative period, we do not believe that low vitamin C levels contributed significantly to the occurrence of these disruptions.

It has also been reported that vitamin B (especially pyridoxine and riboflavin) and vitamin K deficiencies may be involved in wound disruption. It is certainly conceivable that hypoprothrombinemia severe enough to initiate hematoma formation might occasionally be responsible for wound disruption. The use of heparin or dicumarol might in similar fashion be responsible occasionally.

Overenthusiastic hydration (particularly if the employment of saline is abused) has been mentioned as interfering with wound healing due to the edema produced.

It has also been suggested that the administration of ACTH and cortisone in large doses may inhibit wound healing by impeding fibroblastic proliferation.[7,38] Savlov and Dumphy[42] produced experimental evidence that cortisone administered preoperatively will diminish the tensile strength of wounds; but once cellular proliferation has begun, cortisone has little or no effect. Cole and his co-workers[5] have recently reported that there is no clinical evidence of adversity on wound healing with the usual doses of these drugs in humans. Certainly this has been our own experience from recent clinical observation.

SURGICAL TECHNIC

Opinions continue to differ on the relative merits of absorbable and non-absorbable suture materials. Even catgut sensitivity or allergy has been cited for responsibility in wound disruption.[26] Whipple has long favored the use of silk in clean wounds, emphasizing a rigid self-discipline to those wishing to use silk. Howes[20] contributed excellent advice to those who preferred catgut with emphasis on necessity of decreasing the size commensurate with the tensile strength of tissue being approximated.

We do not believe that the type of suture material plays any role in wound disruption, provided that all due consideration is given to suture size and handling technic, and that the suture material holds the tissues approximated long enough to permit the wound to develop its own tensile strength. It so happens we personally prefer non-absorbable suture materials, particularly stainless steel wire and an interrupted technic. We prefer wire, not because of its strength but because we are convinced it excites virtually no tissue reaction. The interrupted technic not only adds safety but also reduces the amount of suture material and degree of strangulation.

In our forty cases neither the type of suture material used nor interrupted or continuous technics employed significantly influenced the incidence of wound disruption. Absorbable suture material was employed in twenty-three instances and non-absorbable suture material in the other seventeen (wire in nine, cotton in six, and silk in two). On the same order, interrupted or continuous technics were employed.

Some surgeons put great faith in retention sutures on a through and through closure. Such sutures are certainly not an unmixed blessing inasmuch as they tend to strangulate tissue and not infrequently encourage infection in the devitalized areas. Retention sutures

placed superficial to the peritoneal layer would appear to offer no advantage over layer closure while exposing the wound to the disadvantages of retention sutures.

Most surgeons eschew the through and through closure of all layers of the abdominal wall for routine closure since it does not provide for accurate anatomic restoration in layers.

No form of routine retention suture offers any assurance against disruption. Thus Mayo and Lee[30] report that 24.5 per cent of their recent cases (period II) had retention sutures, a figure very similar to ours. In our series retention sutures were employed in eight instances (20 per cent of our disruptions).

The incidence of wound disruption in Wolff's[61] series in cases in which retention sutures were used was 3.2 per cent. Glenn[10] reports an incidence of 1.29 per cent in cases in which closure was with through and through silver wire.

One thing that impressed us in this study was the all too frequent inability to determine from the records whether or not the surgeon delegated the closure to one of his assistants. We have no proof to support our impression, but we do believe that not infrequently the closure is considered an anticlimax to the operating room proceedings and fails to hold the surgeon's interest. The surgeon then delegates the closure to his assistants. This may be entirely proper, provided that he is absolutely certain about his assistant's ability, devotion and caution. These cannot be determined without considerable personal supervision, where the surgeon assumes the assistant's role until he is certain that this is no longer required. The surgeon who elects to "blame" the occurrence of a wound disruption on his assistant who closed the wound deserves nothing but censure.

PROPHYLACTIC MEASURES IN WOUND DISRUPTION

Although it may not always be possible (because of the urgency of the situation), in most instances it remains in our power to modify many of the factors even remotely affecting the possibility of wound disruption. Since they concern so many aspects of adequate pre- and postoperative care, a thorough discussion is beyond the scope of this article.

In the preoperative phase changes in body chemistry can frequently be corrected, hydration status improved, diminished vitamin stores replaced, diabetes brought under control, and chronic pulmonary disorders improved by postural drainage, bronchial tree aspiration and breathing exercises, so as to minimize the pernicious impact of repeated protracted coughing.[11] Infection can often be controlled, protein and hemoglobin deficits restored, and tissue tone maintained by activity. In the chronically malnourished patient who is unable to eat satisfactorily, jejunostomy under local anesthesia may offer the only means of preparation of the patient. In the presence of distention, preoperative consideration (time permitting) should be given to decompression either by intubation or proximal surgical decompression, depending upon the urgency and nature of the situation. Only in rare instances (in our experience) is it possible to reduce the obese patient's weight. It is incredible how impervious the obese candidate for surgery (for even elective procedures) remains to all forms of threats, flattery, cajoling or shaming.

During abdominal operations the value of the nasogastric tube should not be underestimated. Such a tube inserted at the beginning of an operation has much to recommend it both from the standpoint of offering decompression throughout the induction of anesthesia and throughout the operation; in addition, however, by minimizing regurgitation it serves to decrease the possibility of aspiration pneumonitis.

Anatomic incisions should have preference over the non-anatomic or vertical incisions whenever possible; and while it is true that wounds heal from side to side, unduly long incisions are more likely to end in wound disruptions than smaller ones, especially if the vertical incision is employed as has been demonstrated by Sloan.[47]

The anesthetic is perhaps less important than the anesthetist. Most surgeons are satisfied if the abdominal wall is relaxed, the viscera tranquil, the heart beating and the respiratory exchange adequate, no matter what agent is used. Bronchial tree toilet should be completed just before closure is attempted, as recommended by Wolff.[61]

Drains should be avoided as much as possible. The old dictum of "when in doubt, drain," might better be paraphrased, "when in doubt, do not drain." Exteriorization of

viscera through the main wound should also be avoided.

Of course the handling of tissue should be merciful at all times; hemostasis should be accurate, suture size minimal and closure of all layers accurate and with minimal tension.

In the postoperative period one should be especially careful to obviate undue muscular strains and distention. Elimination of coughing is largely a matter of prevention of pulmonary complications. Deep-breathing exercises, frequent turning and early ambulation help in this consideration. Heavy sedation and narcosis contribute to the occurrence of pulmonary complications. Patients can be taught and encouraged to expectorate without employing a violent cough to do so.

Increased intra-abdominal pressure is best avoided by prophylactic nasogastric suction. It is not enough to have the tube down; it must be working. Time and again on rounds one sees a patient on nasogastric suction with an emesis basin close at hand; investigation will reveal that either the tube is plugged or coiled, a piece of tubing has become detached, the apparatus is defective or the current is turned off the suction apparatus. Constant personal vigilance is required to avoid these annoying failures. Recent experiences have convinced us, too, that plastic tubes are not as well tolerated as rubber tubes; we have observed on several occasions that such tubes elicit a tough, tenacious mucus that repeatedly and promptly seals the openings. Rubber tubes should not be so flaccid that they collapse under the slightest negative pressure. We have also come to avoid the various long tubes in paralytic ileus. In our experience they invariably worsen the situation. A short tube (Levin tube) is much more efficient in these situations and infinitely easier on the patient. To have the long tube propelled there must be some active peristalsis; the more active it is, the easier the passage of the tube.

We have a personal abomination for enemas, flushes and rectal tubes, and decry their enthusiastic routine usage. A bowel temporarily paralyzed after abdominal surgery and distended because it is unable to handle the load it is already carrying will be better relieved by giving it nothing to do and aspirating air and gastric secretions at the proximal end to lessen its load; this is better than abusing the bowel by increasing its burden with enemas and flushes through the distal end. When the bowel has recovered, it will expel flatus effectively; the abdomen will be flat and the patient hungry. Once the patient is eating, food residue provides an excellent "cathartic" and the bowel will function without enemas or flushes. Early ambulation is an excellent aid in expelling flatus.

Singultus should receive prompt attention because of its persistent, powerful strain on the wound and debilitating effect on the patient. Gastric dilatation, uremia, peritonitis and cardiac enlargement should be excluded.

If any of the foregoing causes are found to be responsible, their prompt correction will probably stop the hiccoughing. If the cause remains obscure, if singultus persists, carbon dioxide inhalations may prove effective, at least temporarily and often completely. The tension must be higher than 5 per cent to be effective. We have on several occasions, all else failing, administered large doses of quinidine with success. Occasionally a phrenic nerve block is necessary.

Urinary distention will occasionally contribute significantly to abdominal distention. An indwelling catheter is preferable to repeated catheterizations.

Throughout the postoperative period one must, of course, keep in mind the possibilities of anemia and dehydration, overhydration, vitamin inadequacy, hidden infection and electrolytic imbalances. In the latter category hypokalemia is especially worthy of mention because it may account for an otherwise unexplained distention.

Early ambulation is not only a safe procedure but also a desirable one since it minimizes so many of the complications responsible for or at least favoring wound disruption (coughing, vomiting, distention and urinary retention).[3,4]

DIAGNOSIS OF WOUND DISRUPTION

Wound disruption of the type being considered here, where there is at least a partial separation of all layers, usually presents no problem in recognition. Occasionally, however, even this type is not easily recognized, and the surgeon observing an agglutinated fibrinous mass of unidentified tissue beneath the separated skin assumes it to be granulation tissue resting upon an intact rectus sheath when in reality it is an agglutinated mass of eventrated viscera.

It is beyond the scope of this paper to consider lesser degrees of wound disruption, involving separation of one or more of the deeper layers. These disruptions of lesser magnitude account for the occurrence of the not inconsiderable frequency of incisional hernias. Certainly it is immediately apparent that essentially the same factors are involved in both and their occurrence should properly be included in the statistics of wound disruption.

Although it is true that occasionally wound disruption occurs in all layers simultaneously, more often it appears to be a gradual process, with the final stage which presents such a dramatic finding on ward rounds leaving the patient singularly free of pain and discomfort.

Indeed, many disruptions of the type we are considering remain concealed until the skin sutures are removed. This probably accounts for the frequent reference in the literature to the observance of their occurrence between the fifth and eleventh days, when in reality a serious separation had probably existed for a considerably longer period. Most wound disruptions probably occurred several days before recognition and perhaps even before the patient left the operating room.

The reason for emphasizing the importance of early recognition of impending or actual disruptions lies in the fact that earlier and prompt repair can be carried out with considerable reduction of morbidity and mortality. Thus Glenn[10] was able to report a reduction in mortality from approximately 45 per cent in his first series to approximately 19 per cent in his second series, essentially due to early recognition.

Excluding the obvious presence of eventration, perhaps the best known premonitory sign of wound disruption is the sudden appearance of a serosanguineous discharge soaking the dressing of a patient who had presumably been making an uneventful recovery. More often than not, close questioning will elicit the fact that this discharge was immediately preceded by a "feeling of something giving way" following an episode of coughing or some other undue strain. Or perhaps the patient will recall the occurrence of this several days earlier.

The complaint of sharp pain in the wound should always call for investigation. If on inspection edema or fluctuation are apparent, or perhaps a knuckle of bowel is palpable beneath the intact skin or the sharp edges of fascial layers that have separated are felt, the diagnosis of wound disruption is not difficult to make provided the surgeon keeps an open mind about this possible eventuality. Although intestinal obstruction may be an immediate contributory factor in wound disruption, occasionally the reverse is observed when a loop of bowel lodges itself between separated wound layers and becomes obstructed. If wire sutures were employed in the closure, a flat plate of the abdomen may prove of value in establishing the diagnosis by revealing a broken and separated suture line.

TREATMENT

In the management of an established wound disruption with eventration one of two methods may be employed: either secondary closure by immediate resuturing or so-called "conservative" management by tamponade.

On the whole, the immediate resuture method when feasible (as is usually the case) is far superior to tamponade.

Occasionally the patient's condition is so critical that immediate resuture is out of the question because of severe shock, because the disruption has complicated generalized peritonitis, or the disruption upon first recognition presents a suppurating agglutinated mass of viscera in a desperately ill patient. The tamponade method is then of real service. As pointed out by Colp,[6] it is the simplest, easiest and least shocking procedure; it can be carried out without anesthesia and without moving the patient from his bed.

The granulating surface or exposed viscera may be covered with fine mesh gauze (preferably impregnated with antibiotic ointment). Additional absorptive gauze fluffs are placed in several layers on top of this; the skin is given several coatings of compound tincture of benzoin and the tamponade is completed by strapping with wide flamed adhesive strips. A firm abdominal binder is applied for additional support.

More often than not it will be impossible to effect satisfactory approximation at the first strapping. However, such a tamponade may be reapplied at intervals of four to six days; and as healing by second intention progresses, succeeding approximations may produce quite satisfactory coaptation.

There are several disadvantages to this method. First, there is always the possibility

of intestinal obstruction or formation of fistula. At best the approximation is insecure and the degree of disruption and eventration may be seriously aggravated, particularly in the presence of unrelieved singultus or a persistent cough. Healing by second intention takes a long time; generally speaking, a minimum of five to six weeks is required. Finally, the late sequelae of a possible mechanical obstruction and almost certain incisional hernia must be considered.

Occasionally the decision is made in favor of tamponade, but reduction is so unsatisfactory that in desperation a secondary closure is attempted some twenty-four to forty-eight hours later, at which time the patient's condition may be more critical and the operation may constitute a greater risk than it would have presented twenty-four to forty-eight hours earlier.

In our series delayed secondary closure was selected in five instances because of failure to attain satisfactory reduction by tamponade. The mortality rate in this group was 20 per cent.

On the whole, closure by immediate resuture is the treatment of choice.[30,33,44,53]

Personally, we believe closure should not be attempted under local anesthesia. At present our own preference is epidural block and an insistence for the services of the most skilled anesthetist available.

We prefer the through and through silver wire closure of all layers of the abdominal wall, as recommended by Reid and co-workers.[40] Although various types of suture materials have been employed, silver wire has proved most satisfactory in our hands because it is readily malleable, non-irritating and possesses sufficient tensile strength.

A large, curved cutting (Hagedorn) needle is threaded on each end of 14 inch silver wire strands (No. 20 gauge). These needles are then passed through the entire thickness of the abdominal wall from the peritoneal side outward. The required sutures are thus placed approximately 1 inch apart and are left untied (with hemostats replacing the needles on the free ends) until all have been inserted. The assistant then gathers the sutures and applies tension while the surgeon makes certain that the loops do not include omentum or bowel. The surgeon then accepts the sutures one after another, twisting each with just enough tension to effect approximation.

One distinct advantage to the use of silver wire in this fashion is that if undue swelling should occur, these wires may be easily untwisted just enough to relieve the tension.

Such sutures are generally left in place a minimum of fourteen days and considerably longer if healing appears delayed.

Some attempts have been made to improve the technic of secondary closure by excision of the disrupted wound margins and resuturing by layer closure. These have not worked out satisfactorily[44] despite experimental evidence that the tensile strength of a resutured wound, tested on the third day, is stronger regularly than that of a similar wound in control animals.[42,43]

In our series there were no redisruptions in the thirty-two cases treated with through and through closure. Layer closure of the type described heretofore was carried out in five instances with two redisruptions.

COMMENTS

Although it is apparent that the contributory factors in wound disruption are multiple and difficult to evaluate, it is our impression from this analysis and a review of the literature that the major factors are less elusive.

Any of the contributory factors listed may be involved to varying degrees in a specific wound disruption. However, we firmly believe that it would be a rare instance to find a disruption in the absence of the major factors considered, so that at best the contributory factors usually exert a diminutive influence. Recent studies of the metabolic response to all forms of injury reveal that the living injured organism bestows a tremendous biologic priority (for the various factors of the common metabolic pool) to the injured part, so that factors such as protein, vitamins, water and the various electrolytes may be available to the injured part even in the face of fairly significant quantitative variations of these factors as reflected in our sampling methods. Because of the remarkable biologic priority assigned to the injured part, these variations do not critically alter the healing process.

It is our impression that the influence of contributory factors in wound disruption has been overemphasized in much of the literature on the subject.

Meleney and Howes[32] epitomize the real problem neatly when they point out that

when a wound is closed, an equilibrium is reached between the approximating force of the sutures and the retraction force of the tissues; and the tension on both sutures and tissues is being constantly altered by the factors we have listed as exerting a major influence in wound disruption (coughing, retching, vomiting, sneezing, singultus, distention and various forms of uncontrolled straining). If this force is great enough, the suture material will break or it may hold but cut through the tissues. Severe infection, in very rare instances, may be responsible by its disintegrating influence on tissue, absorbable suture material or both.

Severe infection, we believe, is rarely the major immediate cause, so that for the most part the problem resolves itself into the ability of suture and tissue material to withstand the tension applied.

Although no type of incision affords complete immunity from the possibility of wound disruption, the anatomic incision (transverse or oblique) affords considerably greater security than all forms of the vertical incision. Sloan's[45] demonstration of a tissue retraction force approximately thirty times as great in the vertical incision under light anesthesia is hard to dispute. We can only speculate how much greater this force disparity may become during such acts as coughing and sneezing.

As pointed out by Singleton,[45] much of the controversy over suture material is due to the surgeon's endeavor to overcome these considerable retraction forces with suture material, when it is not the closing of an incision, as emphasized by Sloan,[48] but the opening that is principally responsible for all degrees of wound separation.

In conclusion, then, we wish to assert that we do not intend in any way to minimize continued vigilance of all the preoperative, operative and postoperative factors discussed. Rather, we wish to emphasize the importance of the major factors concerned with wound disruption and, more particularly, the distinct advantage of the anatomic incision in this respect, even though its fashioning and closure are more tedious.

SUMMARY

The incidence, etiology, mortality, prevention, recognition and treatment of abdominal wound disruption with eventration are reviewed.

Forty cases of wound disruption occurring in 11,334 laparotomies during a five-year period are presented.

Increased intra-abdominal pressure, muscular strain and wound infection are cited as the major causes of wound disruption.

In the prevention of wound disruption the more frequent use of the transverse (or anatomic) incision is recommended.

In the management of disrupted wounds with eventration immediate resuture by through and through closure is recommended as the treatment of choice.

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DISCUSSION

Jack M. Farris (Los Angeles, Calif.): I should like to congratulate Drs. del Junco and Lange on the excellence of their presentation.

I share Dr. Lange's enthusiasm for the use of non-absorbable stainless steel wire sutures and also for the use of the transverse anatomic incision, although I am sure he will agree one must avoid overemphasizing these features because of the multiplicity of those involved. I have employed interrupted stainless steel No. 32 wire for the closure of fascial layers in all major laparotomies for the past eighteen years. Wire possesses the advantage of being physiologically inert, inducing a minimum of tissue reaction; and in the event that infection intervenes one is not confronted with the problem of extrusion of sutures as is the case in cotton or silk. The advantage of wire is in no way related to its increased tensile strength but rather to the minimum of tissue reaction with an early onset of fibroplasia.

Ample precedent has been set for the use of metallic sutures since preantiseptic days and one need have little fear that their use constitutes an unacceptable surgical procedure. In the 16th century, Hironamus, a teacher of Sir William Harvey, extolled the advantages of wire in the surgical ligation of blood vessels. Henry S. Levert of Alabama in 1829 reported a series of experiments on dogs with successful ligation of carotid and femoral vessels with wire. A pioneer in the use of metallic sutures was J. Marion Sims who successfully closed a vesicovaginal fistula with wire suture after thirty previous unsuccessful attempts. He was aided in this endeavor on November 14, 1848, by a jeweler, blacksmith and dentist, who joined him in the celebration of this surgical triumph. Dr. Babcock of Philadelphia began the use of metallic sutures in 1904, and in 1932 turned to the use of alloy stainless steel wire.

A series of experiments have been conducted during the past year with the collaboration of Dr. Harry Davis in an effort to study some of the factors concerned in wound disruption. The most interesting feature of wound disruption is the fact that a second one rarely occurs. This suggests that there is no "lag period" at the time of the secondary suture. Experiments carried out on rabbits designed to measure the force necessary to produce rupture of the wound indicate that a wound seven days old in the rabbit will regularly rupture at levels in the neighborhood of 60 mm. of mercury as measured by an inflatable intraperitoneal balloon. If the wound is simply resutured by through and through technic and seven days allowed to elapse, the pressures now necessary to produce rupture of the wound are in the neighborhood of 170 mm. of mercury; and in one animal 300 mm. of mercury were necessary to produce disruption. This observation suggests that an extract of a traumatic wound injected into the rectus muscle of an animal prior to the primary operation might achieve accelerated tensile strength similar to the secondary suture of a disrupted wound.

Siegfried F. Herrmann (Tacoma, Wash.): I have enjoyed this presentation very much but I must say it has not helped me a great deal. I stand as one who has had, unfortunately, great experience with wound disruption and I am convinced by this time that the fault, usually at least, does not lie with the surgeon. If a surgeon can suture 200 or 300 abdominal wounds without having any disrupt and suddenly wound disruption occurs, it certainly is not because the surgeon does not know how to close the abdomen. There is something else. The factors have been brought out, and I believe the chief factor is something which the patient does. The patient strains, as has been pointed out, and disrupts the inner layers; a wedge of momentum comes through the peritoneum which has been torn open, and then the process continues.

We can blame our anesthetists to some extent for these wound disruptions because, as I observe it, the anesthesia is often so light at the conclusion of surgery that the patient is wide awake and is straining and struggling, not actually keeping quiet as he should. I have seen the beginning of wound disruption on the operating table at the conclusion of surgery. More often it occurs after the patient is in bed and strains, retches, coughs and rips open what we have done.

What I want to point out is that when I resuture these wound disruptions by the simple, interrupted mattress suture technic of wire through and through—it is an on-end mattress suture—there is never a recurrence of the wound disruption. That is not because some extract developed in the tissues. I think it is because the patient is then aware of his abdominal wall and is not going to strain again. I am serious about this point. I believe that if retention sutures are placed, the patient feels it when he does these violent maneuvers and he is not going to disrupt the wound.

When I discussed this with Dr. Claude Welch of Harvard two years ago, I said, "I seldom had disruptions and I have had two in the last month." When he answered that something was wrong, I asked what it was. He said, "Do you use retention sutures"? and I said, "Rarely. Of course, I always use them when I have a disruption to fix and do it under a local anesthetic and they never break open

again." He said, "You put in retention sutures and you won't have wound disruptions." I believe that is right although the chart shown by the authors did not seem to indicate it.

I believe if you make the patient aware of the fact that something hurts when he does something he should not be doing, you will not have wound disruptions.

HENRY J. LANGE (closing): In answer to Dr. Herrmann's satisfaction with reclosures and retention sutures, may I point out that the greatest incidence of wound disruption in our gallbladder group occurred in the hands of men who routinely employ retention sutures for closure. The observation that wounds do not disrupt following their resuturing has been made many times, and I think perhaps the answer lies in the fact that when a wound disrupts everyone on the ward is suddenly alerted and it is as though the "first-team" moved in. The factors that produce abnormal strains upon the wound are relieved and perhaps the closure is made a little more accurately. Many times a surgeon, at the end of a long operation, is bored with the closure. The dramatic sequence of events is over and he regards the closure as relatively unimportant and delegates it to one of his colleagues, who may or may not be adequately prepared to effect a satisfactory closure.

I would like to emphasize one point as regards the various biochemical factors concerned in wound healing (such as anemia, protein depletion, low ascorbic acid levels, etc.). It is occasionally said that wound disruption is the patients' "fault" because he was deficient in one or more of these factors. There is little to support this conclusion, for the recent observations on metabolic responses to injury demonstrate that the living organism imparts a tremendous priority to the injured part for the various factors of the common metabolic pool, so that even in the presence of considerable anemia or serum protein depletion, for example, healing will go on quite satisfactorily and the only detectable difference will be slight prolongation of the lag phase.

The Technic of Heart-Lung By-pass with a Pump Oxygenator

PHYSIOLOGIC STUDIES

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EXTRACORPOREAL circulation for surgery of the heart has now come of age. It was first applied successfully by Gibbon[1] in animals and has now been used in patients by him[2] and by several others, notably at the University of Minnesota and the Mayo Clinic.[3–5] However, although heart-lung by-pass has now become an accepted surgical procedure, the technic is not yet standardized and is still undergoing improvement and simplification. It is the purpose of this paper to describe our technic and experiences in more than 150 perfusions of dogs, and one human case.

APPARATUS

The pump oxygenator that we are now using will be separately described in detail. It consists essentially of two air-driven glass blood pumps especially designed for minimal turbulence, and an artificial oxygenator consisting of a battery of fluted glass plates over which the blood passes in a thin film. No foam is present anywhere in the circuit. We believe this apparatus to be less damaging to the blood than any other type yet described. (Figs. 1 to 3.)

The volume of blood in the machine is held constant by a gravity leveling system which does not require electronic controls. About 1 to 1½ L. of blood is needed to fill and prime the apparatus, but this depends on the expected rate of flow; normally 1,500 cc. blood are required for a dog weighing 30 kg. Oxygen is warmed and humidified before it enters the mechanical lung, and 5 per cent carbon dioxide is added; if this concentration is maintained, no monitoring of the blood pH is necessary.

The blood temperature is maintained by a warming jacket over part of the circuit, and the maximum flow is about 2½ L. per minute at a pressure of up to 300 mm. of mercury at the pump. The larger the arterial catheter delivering blood, the less pump pressure required.

STANDARD PROCEDURE

Mongrel dogs were used, varying in weight from 5 to 25 Kg., and were anesthetized with intravenous pentobarbital sodium. The donor blood used to prime the apparatus was collected the morning of the operation. Heparin was given to the donor dog in a dosage of 2.5 mg. per kg. body weight, and 20 mg. per L. of blood was added after its collection. The apparatus and tubing were filled with isotonic Ringer's lactate solution containing 15 mg. of heparin per L. This heparin was added to the saline to prevent the clotting which was sometimes found to occur at the interface of saline and blood when the saline was replaced with donor blood just before perfusion.

A femoral artery and vein were cannulated for continuous direct recording of pressures; the chest was opened and the heart exposed. The animal was given heparin in a dosage of 2.5 mg. per kg. of body weight before any of the cannulas were placed. Two soft plastic cannulas of approximately ¼ inch diameter were then introduced through purse-string sutures in

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the right atrium, so that their tips lay well within the inferior and superior venae cavae. The largest possible plastic whistle-tipped catheter was placed in the right or left subclavian artery. (Loose tapes were placed around the venae cavae to be tightened when the perfusion began so as to divert all the caval blood into the apparatus.) The cannulas were clamped and their outlets allowed to drain into the venous reservoir of the apparatus. The vertical placement of the outlets of these catheters is important because this largely determines the venous pressure of the animal during perfusion; they could be raised or lowered in order to keep the venous pressure constant, but heart level was usually found to be satisfactory. Another catheter was threaded through the azygos vein into the right atrium so as to collect the major portion of the coronary return. At this time the apparatus was filled with about 1 L. of donor blood, the pumps were started and the perfusion slowly begun. The two caval catheters were then opened, but the tapes around them were not tightened until the blood was flowing freely from the catheters to the machine; they were then cautiously taken up, one at a time, over a period of one minute. Finally, the azygos catheter was opened so that all the venous return was diverted from the heart to the machine.

We believe that this period of almost total by-pass of the unopened heart should be brief. Such coronary return as is not collected by the azygos catheter passes through the lungs and out through the left ventricle. As it issues into the aorta, a large part of it is pumped back into the coronary vessels so that a continuous recirculation of the same blood continues through the myocardium and this builds up toxic levels of metabolites.

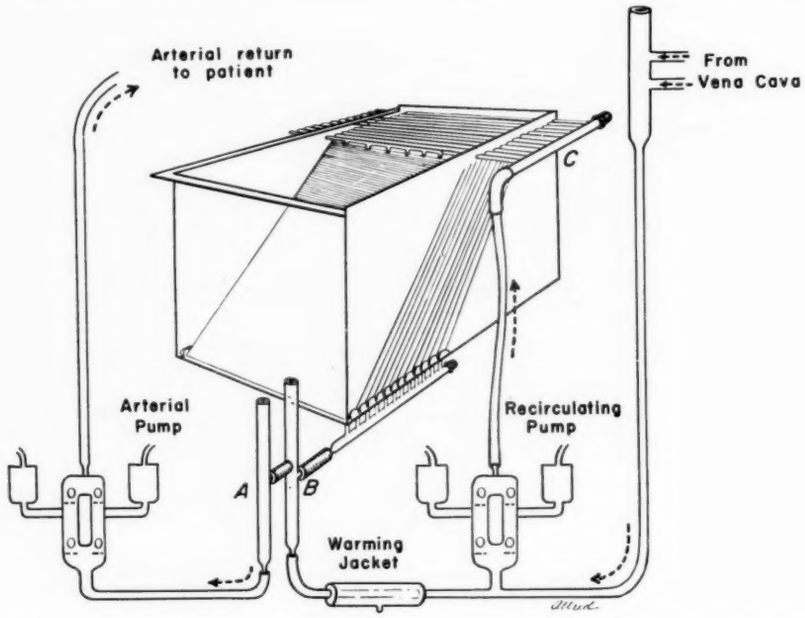

FIG. 1. Schematic diagram of pump oxygenator showing battery of slanted glass plates over which blood is continuously filmed at a constant rate by a recirculating pump. When blood is added to the circuit from the venae cavae, an equivalent volume of blood passes through shunt "A" to be returned to the arterial system by a separate pump.

Providing the perfusion seemed to be going well, traction sutures were placed in the right ventricle and a wide incision was rapidly made. (Once the right heart is opened, vicious recirculation through the coronary vessels is no longer a problem so procedures inside the ventricle can be carried out at leisure.)

Air embolism during closure of the ventricle was prevented by allowing it to fill completely with coronary blood before tying the final suture.

As soon as the ventricle was closed, total by-pass was discontinued but sudden changes were avoided. First, one of the vena caval tapes was slowly released and then the other one minute later; this prevents the blood, which

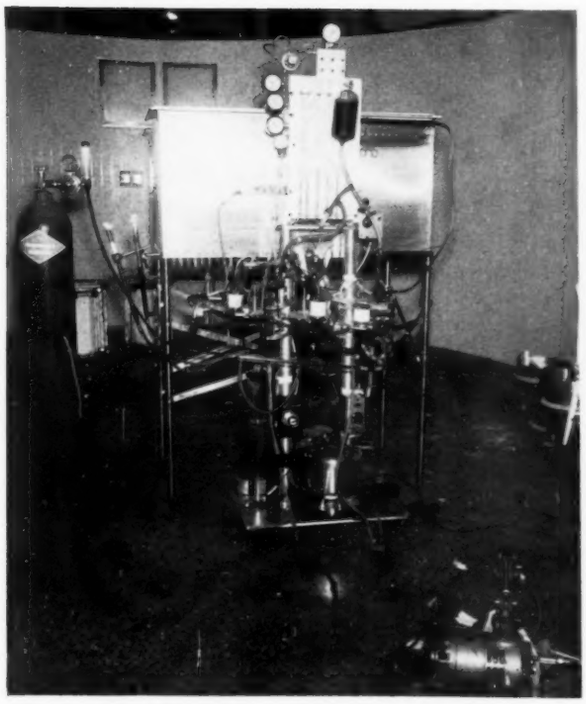

FIG. 2. Mechanical lung and pumps in place in the operating room.

has been lying stagnant in the lung and has become alkaline, from being pumped suddenly through the heart into the coronary vessels and perhaps initiating ventricular fibrillation.

The next step was neutralization of the heparin by the administration of protamine.[6] We have been impressed in our laboratory by the toxicity of an excess of this drug. It may cause a prolonged coagulation time, shock and a drop in platelets; therefore, in order to estimate the minimum dose with some accuracy we have developed a modified titration.[7]

Immediately after the machine has been disconnected, a sample of blood is obtained from the animal and placed in a series of tubes containing various concentrations of protamine. Fifteen minutes later inspection will show which tube, with the least amount of protamine per milliliter of blood, has clotted within a normal time interval. This amount of protamine, multiplied by the estimated blood volume of the animal, provides the required minimum dose. The injection should be made very slowly in order to prevent shock and loss of platelets.

PHYSIOLOGIC FINDINGS

Due to shortage of staff we have often not attempted to maintain sterility, and as a result

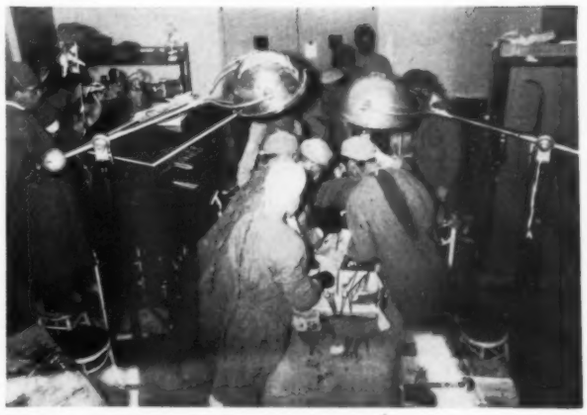

FIG. 3. Apparatus in use during closure of ventricular septal defect.

have anticipated secondary infection. We have considered as a recovery any animal that appeared well, behaved normally and ate well for the first two or three postoperative days. Of our "recovered" animals, about one-half ultimately died from infection, often empyema. The duration of perfusion has usually been about one-half hour and our longest heart-lung by-pass lasted for two and a half hours with the pulmonary artery clamped.

RECOVERY

Of the last fifteen consecutive dogs subjected to total by-pass, nine recovered, four died due to a surgical error and two died from severe bleeding. One of these two had severe thrombocytopenia before operation and the other received inadequate protamine. Hemolysis was very slight and frequently could not be measured since in many animals the plasma hemoglobin after perfusion was less than that of the donor blood before perfusion. Blood flow during perfusion was usually about 70 cc. per kg., and arterial pressure between 70 and 90 mm. Hg. Almost all of these animals were subjected to right ventriculotomy, and in six of them a piece of ivalon sponge was sewed into the wall of the right ventricle.

COMMENTS

It is well known that hemorrhage and other complications following the extracorporeal circulation of blood are closely connected with the degree of trauma to the blood in the mechanical system.[8] Turbulence, jets and foaming appear to be associated with red and white cell destruction, and with the loss of

platelets. As previously mentioned, our circuit has been specially designed to avoid this type of trauma. The extent of our success is shown by the results of our longest total by-pass (two and a half hours) in which after two hours, the platelet count was 150,000 and the white cell count 8,050. This animal remained in excellent condition and made a complete recovery. We do not know the theoretic limit of total by-pass but it is at least several hours, and perhaps eventually it may be much longer. In any case, the totally perfused animal is essentially normal while the perfusion is going well—reflexes and movements are unchanged, the heart rate is normal and there are few changes on the electrocardiogram. Under these circumstances there is time, and even leisure, for prolonged operation in the open heart.

We have found it essential to operate with a team that is accustomed to working together and is well acquainted with perfusion technics. In the four animals described as dying through "surgical error," the error in each case was due to unfamiliarity with the specialized technics of perfusion on the part of a new member of the surgical team.

We have now entered the stage of clinical trial and have operated upon a two and a half year old child with a large interventricular septal defect. He had been on the verge of cardiac failure, and catheterization showed a pulmonary hypertension of 75 mm. Hg. There was a considerable left-to-right shunt which seemed to justify an attempt to close the defect.

An extracorporeal heart-lung by-pass was carried out for eighteen minutes, during which time the right ventricle was open for eleven minutes. The defect was high under a flap of the tricuspid valve and was closed by direct suture. The operation was completed and the patient returned to the ward in fair condition, but unfortunately a bundle branch block developed which was followed by increasingly severe nodal arrhythmia and the patient died about five hours postoperatively.

At autopsy the defect was found to be completely closed, but the right ventricle was large and the pulmonary artery was thickened and arteriosclerotic. In retrospect, it is likely that had we known how severe were the changes caused by the pulmonary hypertension we might not have accepted this patient for operation. We attributed his death to postoperative cardiac failure associated with a high fixed pulmonary resistance, but there is always a great risk in closing such a defect in the presence of severe pulmonary hypertension. It is interesting to note that there was no postoperative bleeding, the platelet count after perfusion was within normal limits, and there was no visible hemolysis.

CONCLUSIONS

A method of heart-lung by-pass which produces minimal changes in the blood has been described.

Experience in one human case demonstrated that this is a practical operating room procedure.

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DISCUSSION

Irving A. Meeker, Jr. (Los Angeles, Calif.): The authors have given an excellent presentation of their experiences employing extracorporeal circulation. Of particular interest and a really significant contribution in this field, I believe, is their meter-

ing type pump and also their very simple and effective means of obtaining venous return from the patient.

In our surgical research laboratory at the University of Southern California (quite independent of their work) we have also resorted to weighing the blood, so to speak, as their pump does in order to obtain an immediate and accurate measurement of the balance between the volume of blood coming out of the animal and that going back so as to avoid over- or undertransfusing of the recipient.

We have also been interested in measuring free venous return at any given moment, and have developed a simple device which is calibrated to show continuously the approximate amount of blood being returned from the venal cavae and the coronary sinus.

The authors indicated they did not employ filters in the circuit they employed. Opinion at present appears to be divided as to the need for them. The objections raised against using filters are that they tend to strain out platelets and cause hemolysis of the red cells. However, because of the factor of increased safety, we have included a large surface, relatively porous filter in the circuit we use. Blood is not forced through it, but instead passes through purely by gravity.

I wonder if Dr. Gerbode would comment on the pumps his group has developed for the circuit they use, and the advantages these have over the more common Sigma motor pump with metal fingers which massage a tube containing the blood and which is being used in many centers throughout the country.

FRANK GERBODE (closing): These experiments are expensive, and require a great amount of interest on the part of the people who are participating in the program. I have been particularly fortunate in working with people whom I consider very highly; I am extremely grateful for their great interest and devotion. In particular, I want to give full credit to Dr. Osborn for suggesting the type of pump which we have used in these perfusion experiments.

Dr. Meeker asked me to comment on the pumps we have developed. I would like to re-emphasize that the pump delivers what it receives; therefore, it is like the heart. It receives a certain amount of blood and pumps out that amount of blood, responding very much like the cardiac chambers in that respect. It also has the additional feature of permitting a transfusion into the system if what it delivers is not sufficient. Flow meters and other devices are not used, thereby reducing trauma to the blood.

Squeezing and bubbling blood may cause serious changes if carried on for longer periods than ten to fifteen minutes. Red cells become damaged, platelets are lost, and there is more likelihood of postoperative bleeding.

Short perfusions can be performed very well with inexpensive apparatus. By this I mean using the Sigma motor pump and one of several types of oxygenators which are quite easy to make. However, if the perfusion is extended to twenty, thirty or forty minutes, the effects of squeezing and bubbling blood begin to show. This may be delayed perhaps a day or two after the perfusion is completed because the damaged red cells die sooner than those in which there has been less damage. We have used filters at times.

One of the best contributions of the group has been the protamine titration technic which was developed largely under the direction of Dr. Perkins. It is quite simple and effective.

The Use of Intravenous Lipoid Substances in Surgical Patients

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From the Department of Surgery and the Surgical Research Laboratories of the University of California School of Medicine and the University of California Surgical Service at the Veterans Administration Hospital, San Francisco, California.

GEYER,[1] in 1948, demonstrated that the experimental animal could metabolize emulsified fat when it was given intravenously. This work was soon confirmed by Lerner,[2] and in 1949 Shafiroff[3] described the successful administration of intravenous fat emulsions to human patients. By 1951 several investigators[4–6] had offered proof of the ability of human patients to metabolize lipid emulsions. Since then intravenous fat emulsions have been used in attempts to improve the nutrition of patients who must have maintenance by the parenteral route. In surgical practice, preparations of fat have been given most often to patients who have recently undergone major surgery. The ability of these lipid preparations to influence the metabolic response to surgery in the immediate postoperative period has been discussed fully by these authors. However, the evaluation of the use of fat emulsion in other phases of the care of surgical patients has not been fully investigated.

During the past eighteen months, a fat emulsion for intravenous use has been studied in our Surgical Laboratories, and more recently it has been administered to surgical patients. The utilization of the fat emulsion by patients in various stages of surgical treatment forms the basis of this report. This study includes observations on the malnourished preoperative patient and on the late postoperative patient; it compares their response to the fat emulsion with that of patients in the immediate postoperative period.

MATERIAL

An intravenous fat emulsion composed of 10 per cent sesame oil in 4.5 per cent dextrose solution with 0.5 per cent lecithin added as a stabilizer was used throughout the study.* The preparation is sterile, pyrogen-free and quite stable. Repeated examinations have shown the size of the fat particle to be less than 1μ. The emulsion is water-like in viscosity and is isoosmotic with the blood. Prior to its administration in humans, the fat preparation was given intravenously to mongrel dogs.[7,8] Four dogs received more than 500 cc. of the emulsion daily for ten days. There was no evidence of hemolysis, as determined by serial hemoglobin determinations. Autopsy was performed at the end of this period and the brain, heart, lungs, kidneys, spleen and liver were examined for evidence of abnormal collections of fat. None was observed. No untoward reactions or fatalaties occurred during the experimental evaluation of the fat emulsion in dogs.

STUDIES IN HUMAN PATIENTS

One hundred twelve infusions of 10 per cent fat emulsion were given intravenously to twenty-seven patients during these studies. Each infusion consisted of 500 cc. of the emulsion. All of the human subjects were adult hospitalized patients on the general surgical services. During the early phase of our study a member of the surgical house staff was in constant attendance. A record was kept of pulse, blood pressure, respiratory rate and temperature during each infusion. All patients' complaints were recorded. Examinations of blood and urine for evidence of hemolysis were

* The 10 per cent intravenous fat emulsion was supplied by Don Baxter, Inc., Glendale, California.

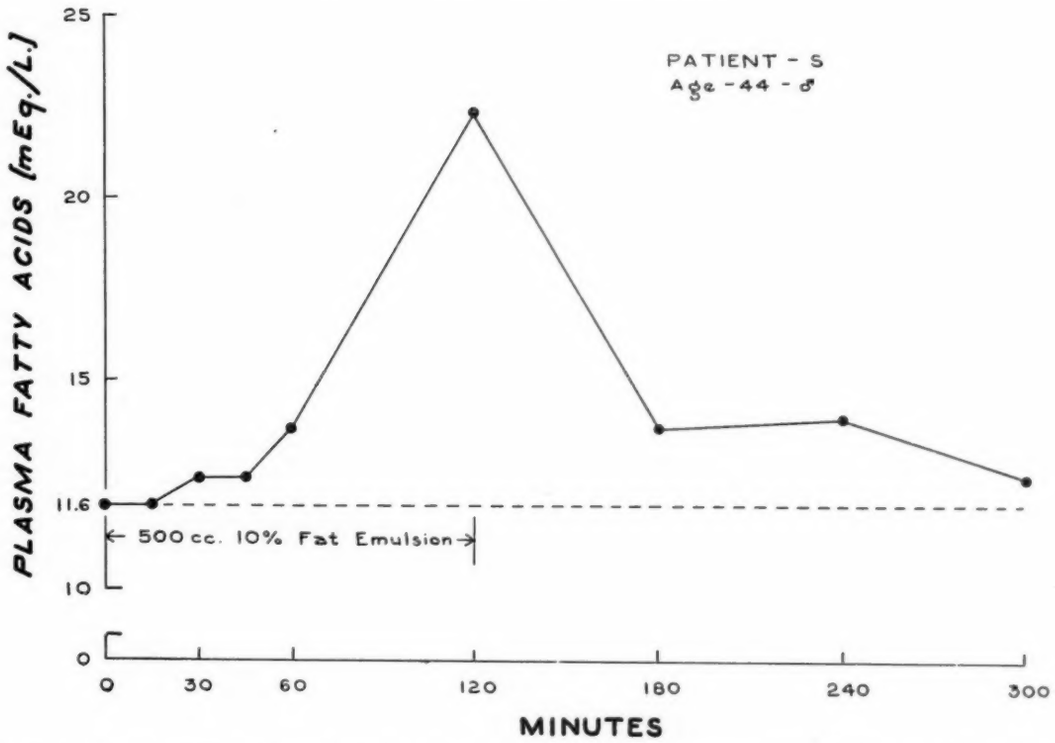

FIG. 1. Plasma fatty acid levels during and subsequent to intravenous administration of a fat emulsion as demonstrated by a graph.

carried out for several days after each infusion of fat emulsion. The rate of intravenous administration of the fat was varied from time to time, and undesirable reactions were tabulated. It was noted that rates of administration which exceeded 175 cc. of fat emulsion per hour were accompanied by a high incidence of undesirable reactions. Very few reactions occurred when the fat emulsion was administered at the rate of 100 to 150 cc. per hour. Table 1 summarizes the incidence of undesirable reactions that were observed in the course of these studies. A rise in body temperature was quite commonly observed. It should be emphasized, however, that in only five patients did a rise in temperature develop that exceeded 1°C. It is significant that these five patients all received the intravenous fat emulsion at rates of administration exceeding 175 cc. per hour. No serious or prolonged reactions were observed at any time, and there were no fatalities.

TABLE 1
INCIDENCE OF UNDESIRABLE REACTIONS IN PATIENTS RECEIVING A 10 PER CENT INTRAVENOUS FAT EMULSION

Type of Reaction	No. of Reactions	Per cent Incidence
Rise in body temperature (over 0.3°C.)	19	17.0
Nausea	6	5.4
Vomiting	2	1.8
Chills	4	3.6
Flushing	3	2.7
Headache	2	1.8
Back pain	3	2.7
Local venous thrombosis	2	1.8
Dyspnea	1	0.9

The rate of disappearance from the blood of the intravenously administered fat after the infusion of 500 cc. of the emulsion over a two-hour period is shown in Figure 1.

When it became apparent that the intravenous fat emulsion was safe for human use, metabolic determinations were started. Four groups of patients were selected and were classified in the following categories:

Group 1. Well Nourished Patients in the Early Postoperative Period. Patients who had just undergone operations that prevented an oral intake of nourishment were selected for the initial study. Each of these patients received 3,000 cc. of intravenous fluids daily.

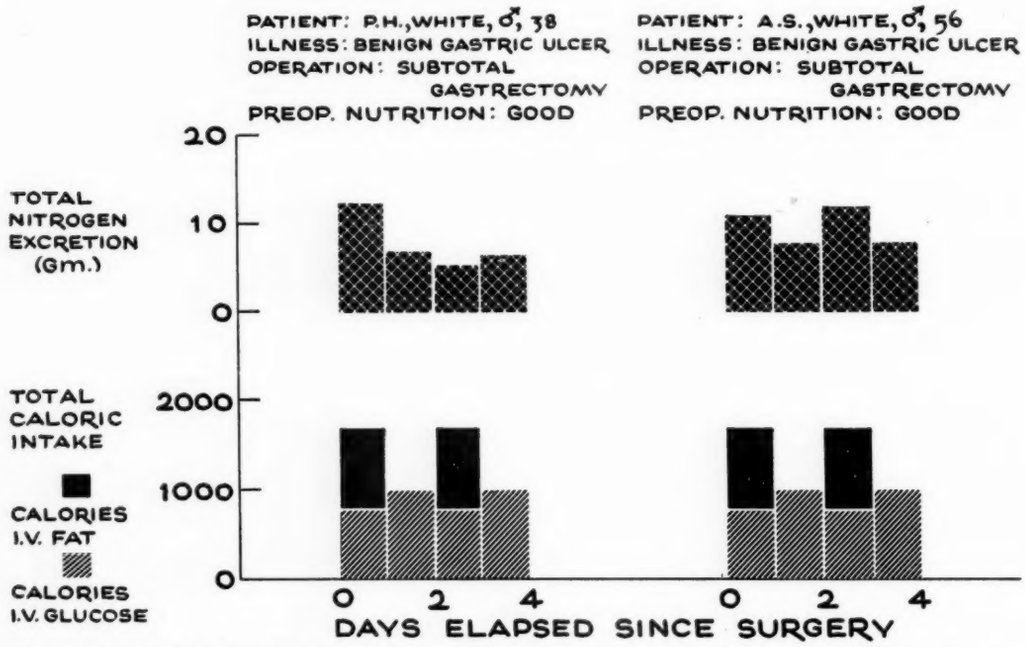

FIG. 2. Graph showing the effect of intravenous administration of fat on postoperative nitrogen excretion in two patients with subtotal gastrectomy.

Infusions composed only of dextrose solutions were given every other day to provide a daily caloric intake of 1,000 calories. On alternate days, 1 L. of 5 per cent dextrose solution was replaced by 1 L. of 10 per cent fat emulsion, thus increasing the daily caloric intake to 1,800 calories. The ability of these patients to utilize these additional calories was evaluated by their effect on the daily excretion of endogenous nitrogen. Since it is well known that the metabolic response to surgery is affected by the magnitude of surgical trauma, subjects undergoing extensive as well as conservative operations were selected for this portion of the study.

Figure 2 is representative of the effect of the intravenous fat emulsion on the metabolic response, in terms of nitrogen excretion, of well nourished patients who had just undergone major operations. The two patients whose studies are tabulated had both had subtotal gastrectomies. It should be noted that the addition of extra calories as a 10 per cent fat emulsion had no significant effect on the nitrogen excretion.

Figure 3 illustrates the daily nitrogen excretion of two well nourished patients in Group 1, one of whom had just had a major surgical procedure and the other, a lesser degree of surgical trauma. It is apparent that the daily nitrogen losses were in accord with the well known fact that nitrogen excretion varies directly with the magnitude of the trauma inflicted upon the patient. The failure of these patients to conserve nitrogen after the addition of extra calories as intravenous fat to their daily intake was again observed.

Group 2. Malnourished Patients in the Early Postoperative Period. The metabolic response to surgery is also affected by the nutritional state of the patient prior to surgery. Figure 4 illustrates the metabolic response, in terms of daily nitrogen excretion, of two patients, each of whom had undergone an extensive operation. One patient was in good nutrition before the operation; the other was malnourished because of chronic illness. The difference between the daily nitrogen excretion of these two patients emphasizes the fact that the loss of body nitrogen in the postoperative period is greater in the well nourished patient. Extra calories in the form of an intravenous fat emulsion, as administered to the patients in Group 1, had no effect on the conservation of body nitrogen in these patients.

Group 3. Patients in the Late Postoperative Period. The contribution of the intravenously administered fat emulsion to the nutrition of the patient in the late postoperative period was then evaluated. Patients were selected

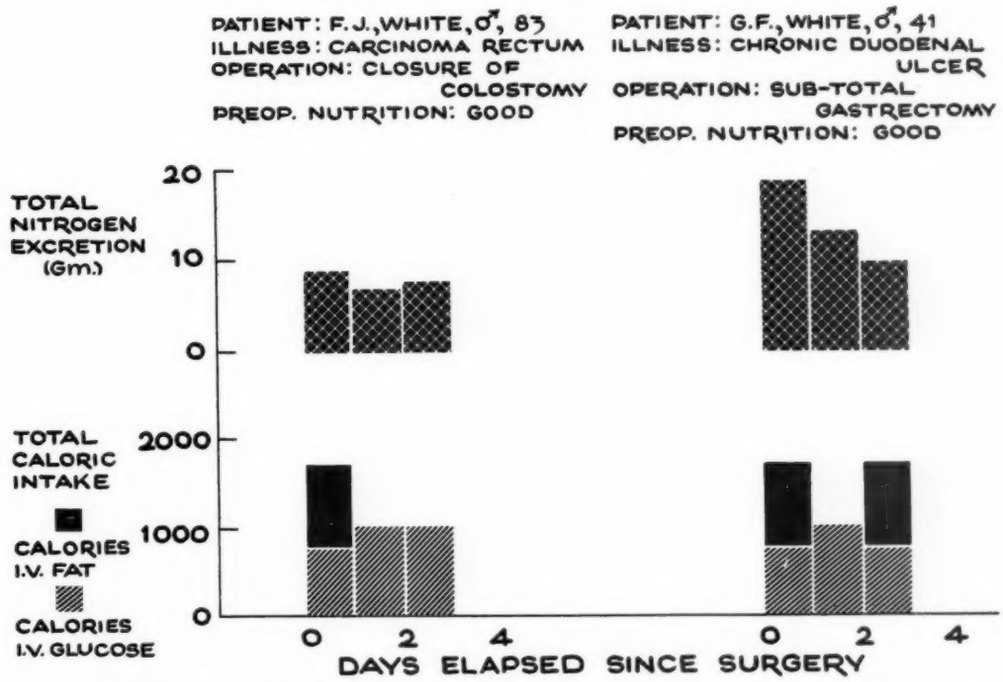

FIG. 3. Graph showing the effect of intravenous administration of fat on postoperative nitrogen excretion in two patients, as related to the severity of the operation.

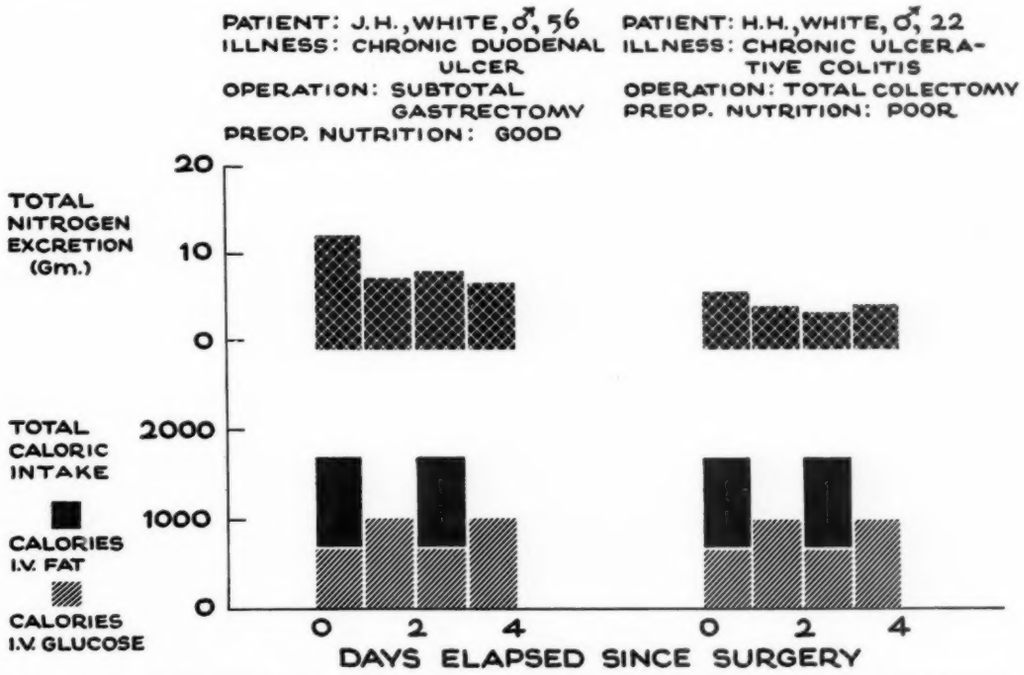

FIG. 4. Graph showing the effect of intravenous administration of fat on postoperative nitrogen excretion in two patients, as related to the preoperative nutritional state.

who had undergone a major abdominal operation at least three days before starting the metabolic study. They were given intravenous glucose solutions exactly as described in the preceding studies. Once again, 1 L. of 5 per cent glucose solution was replaced on alternate days with 1 L. of 10 per cent fat emulsion, and the effect of the added calories on the excretion of endogenous nitrogen was studied.

Figure 5 demonstrates the metabolic re-

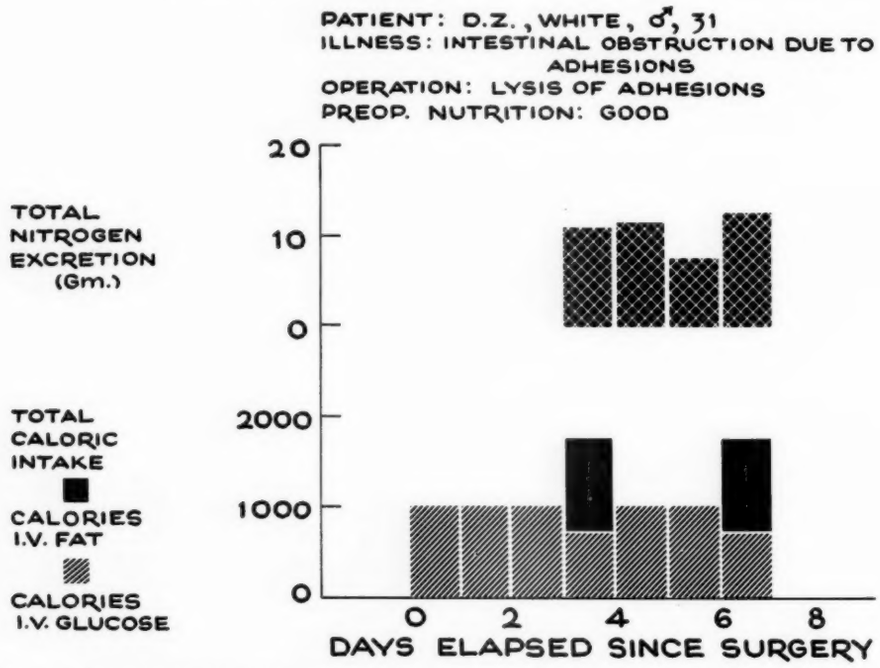

FIG. 5. Graph showing the effect of intravenous administration of fat on the postoperative nitrogen excretion when given several days after a major operation.

sponse to intravenous fat of a patient studied several days after a major operation. His daily nitrogen excretion, like that of patients immediately after operation, was also unaffected by the addition of extra calories as intravenous fat to his daily caloric intake.

Group 4. Patients in the Postoperative Period Who Were Given Exogenous Nitrogen in Addition to the Fat Emulsion. A fourth group of patients was given 1 L. of fat emulsion and sufficient dextrose solution intravenously to provide about 1,700 calories daily. In addition, exogenous nitrogen in the form of an amino acid hydrolysate* was administered intravenously each day, and the ability of the fat emulsion to promote nitrogen retention was observed.

Figure 6 illustrates the daily nitrogen excretion of a postoperative patient who was given 6 gm. of nitrogen as an intravenous amino acid hydrolysate daily in addition to 1,000 cc. of a 10 per cent intravenous fat emulsion. It may be observed from this illustration that almost all of the exogenous nitrogen was excreted, even as late as the eighth postoperative day.

Group 5. Malnourished Preoperative Patients. Finally, the effect of the fat emulsion on the metabolism of malnourished preoperative patients was studied. Patients were selected who were unable to eat an adequate diet because of their disease. Each patient selected his own diet for a control period of several days, and his nitrogen intake and output were determined daily to evaluate the status of his nitrogen balance. After this control data had been obtained, 1 L. of 10 per cent intravenous fat emulsion, 6 to 8 gm. of amino acid nitrogen, and 600 cc. of 5 per cent dextrose solution were given intravenously each day in addition to the oral intake selected by the patient. The effect of these added calories, mainly in the form of fat, was then determined by measuring nitrogen retention.

Figure 7 illustrates the results obtained with a patient in the preoperative period who was malnourished because of chronic illness which prevented her from eating adequately. After a control period of four days, during which a progressive weight loss occurred, the oral caloric intake was supplemented daily with intravenous amino acids and intravenous fat emulsion. The effects of exogenous nitrogen and extra calories on the nutrition of the patient were reflected as a gain in weight. Their effects on her daily nitrogen excretion are summarized in Figure 8. Positive nitrogen balance has replaced the negative balance of

* Parenamine,® courtesy of Winthrop Laboratories, New York, New York.

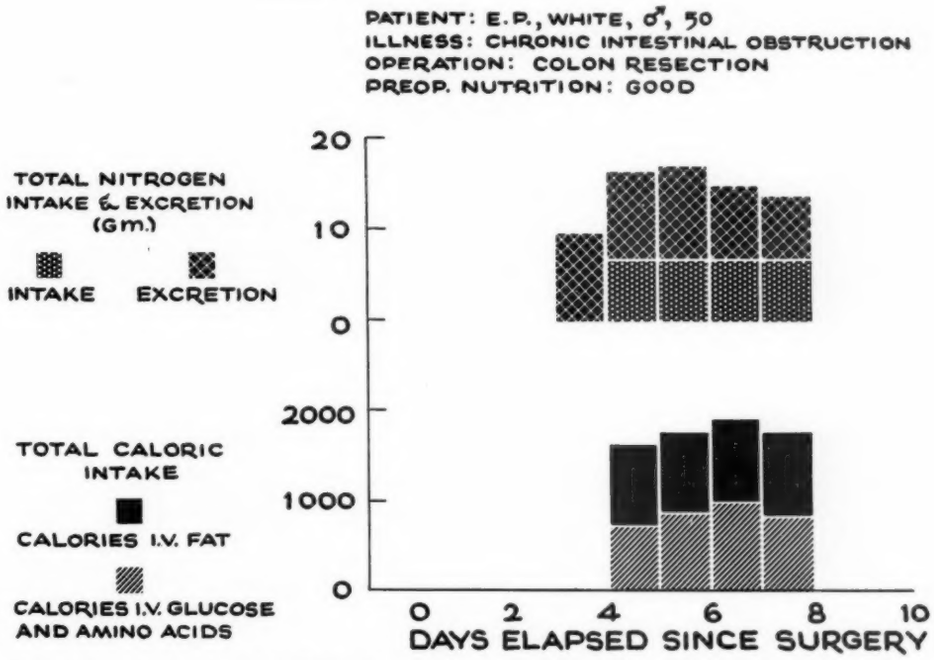

FIG. 6. Graph showing the effect of intravenous administration of fat on the postoperative nitrogen excretion when exogenous nitrogen was supplied as amino acids.

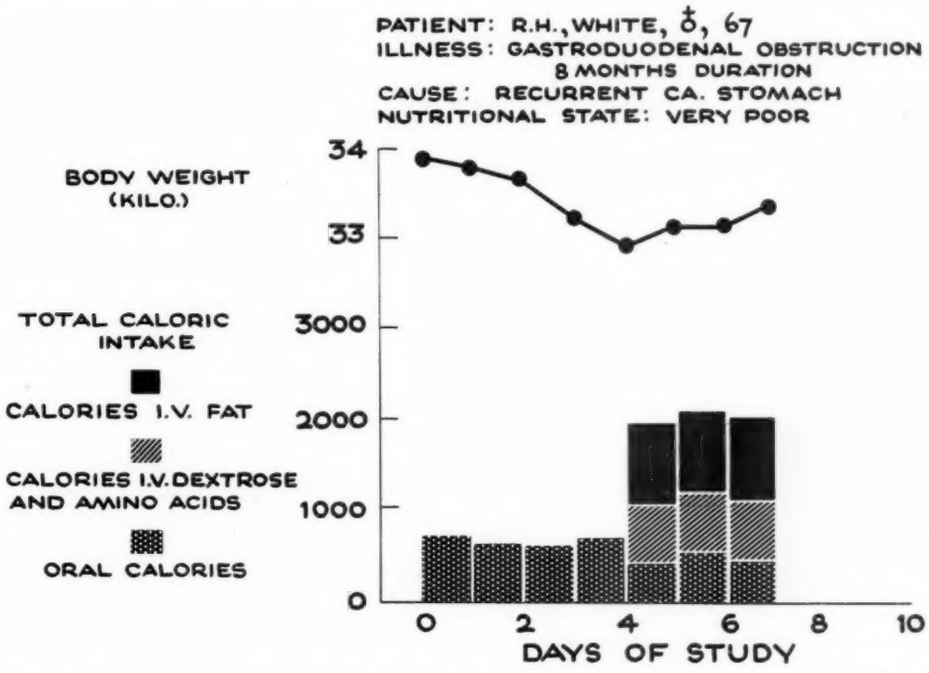

FIG. 7. Graph showing the effect of intravenous administration of fat on the weight of a malnourished preoperative patient.

the control period. It is significant that the daily nitrogen excretion remains almost constant throughout the study. This observation indicates that the extra calories provided by the fat emulsion have been utilized to spare entirely the exogenous nitrogen intake.

The studies in these five groups of patients indicate that this 10 per cent fat emulsion for intravenous use apparently is safe for human administration. A rather high incidence of febrile reactions occurred during the administration of the emulsion, but these reactions

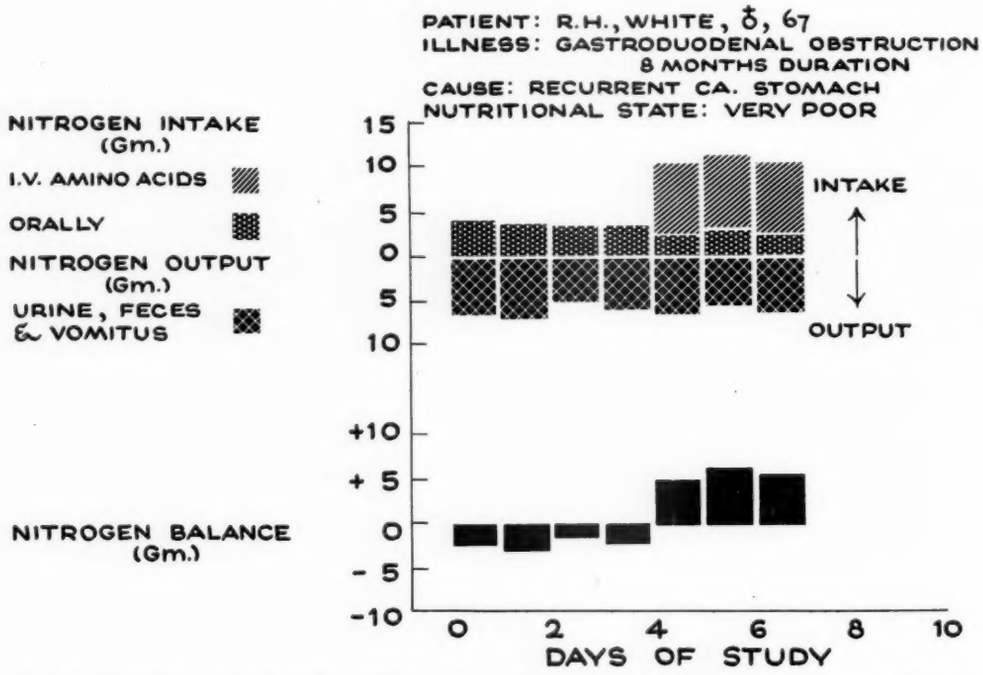

FIG. 8. Graph showing the effect of intravenous administration of fat on exogenous nitrogen retention in a malnourished preoperative patient.

were minimized and reduced in frequency if the rate of administration was kept below 150 cc. per hour.

In the immediate postoperative period the provision of extra calories in the form of the fat emulsion did not affect the loss of endogenous or exogenous nitrogen. This was true regardless of the preoperative nutritional state of the patient and of the magnitude of surgical trauma to which he had been subjected. Thus, it would appear that in the immediate postoperative period the use of intravenous fat emulsions has no significant influence on the conservation of nitrogen. However, the effect of the additional calories from fat in decreasing the postoperative weight loss warrants further study.

A substantial contribution of the fat emulsion to the nutritional welfare of patients during the preoperative period was indicated by our experiments. These patients utilized the fat emulsion readily and they conserved nitrogen as a result of the administration of the fat preparation.

SUMMARY

1. A 10 per cent fat emulsion for intravenous use has been evaluated experimentally and clinically during the past eighteen months.

2. The preparation has proved safe for human administration.

3. The incidence and features of undesirable reactions to administration of the emulsion are described.

4. The effect of the administration of an intravenous fat emulsion on the nutrition of the postoperative patient has been evaluated.

5. Similar studies on the effect of the fat emulsion on the body weight and nitrogen excretion of malnourished, preoperative patients are also reported.

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DISCUSSION

H. J. McCorkle (closing): It has been my privilege to observe the work of Drs. Hine and Harper on the metabolic and nutritional effects of intravenous lipoid substances over the past two years. These studies were properly started with investigations on the utilization of intravenous lipoids by laboratory animals (dogs) and then applied to the evaluation of the metabolic and nutritional effects of intravenous fat therapy on hospitalized patients, some of whom were on my surgical service.

It is apparent from the studies of Drs. Hine and Harper that intravenous fat therapy is not necessary for the routine care of patients who have relatively short convalescent periods in which they are able to take food by mouth within a very few days after operation. In such cases the postoperative fluid therapy now almost universally routinely employed is adequate.

However, for patients who have a long period of hospitalization, during which they are unable to take food by mouth, the advantages of using this high caloric fat solution intravenously, together with amino acid solution and glucose and correct electrolyte solution, is apparent.

Harold A. Harper (closing): It is gratifying to note the ever-increasing interest of surgeons in the nutritional welfare of their patients. The problem of adequately nourishing such patients is complicated by the circumstances which surround most surgical cases. Frequently the gastrointestinal tract cannot be used to feed the patient, or the amounts of nutrients that can be taken and assimilated are inadequate. When the intravenous route must be used as the only means to maintain the patient, the requirements for water and for salts ordinarily may be easily met, but the provision of satisfactory amounts of other nutrients has been difficult or impossible. An important advance in parenteral nutrition was made when amino acids for intravenous administration were made available as a means to supply the building blocks for the synthesis of protein in the body. Their use has been disappointing in many instances because of inability to administer enough non-protein calories to spare maximally the amino acids for protein synthesis. Consequently, the necessity of providing additional calories in parenteral feeding became an essential prerequisite to the satisfactory utilization of amino acids.

The use of hypertonic solutions of dextrose or fructose as well as the addition of small amounts of ethyl alcohol to the intravenous regimen have not solved the problem. In the case of hypertonic sugar solutions their continued use is likely to contribute to the production of phlebitis unless administered very slowly and in a large vein. The physiologic efficiency of calories derived from alcohol is still a matter for debate and in 5 per cent concentrations, the maximum which is recommended, only 280 calories are thus added to 1 L. of an intravenous infusion. All of these considerations have served as a stimulus to investigations on the suitability of fat emulsions as a source of calories in intravenous feeding.

The production of stable and safe emulsions that could be produced in commercial quantities was not an easy task, but when such emulsions were made available for clinical study a proper evaluation of the contribution of lipid emulsions to the nutrition of the surgical patient could be attempted. In the studies reported herein, the value of supplying additional calories with fat emulsions to the patient in the immediate postoperative period has been appraised in terms of their effect on reducing the loss to the body of endogenous or exogenous nitrogen. Probably as a consequence of the unique metabolic circumstances of this period, it appears that the provision of additional calories in any practicable amount does not significantly alter the protein catabolic response. The importance of these additional calories in reducing the postoperative weight loss which should otherwise result from the extreme caloric deficit is, of course, another factor to be considered in a complete evaluation of the use of lipid emulsions during the immediate postoperative period.

When the metabolic effects of trauma and stress have abated, it would be expected that the importance of amino acids and adequate calories in an intravenous regimen could best be demonstrated. The present studies show this well and emphasize the great value of these nutrients in maintenance by the intravenous route of those patients who cannot otherwise be properly nourished. Further studies with this type of patient will undoubtedly confirm this impression. We can then expect a resurgence of interest in the use of parenterally administered amino acids for those cases in which the gastrointestinal tract cannot be used. For such problem cases the availability of a fat emulsion for intravenous use is a substantial advance in the care of surgical patients.

Surgical Implications of Solitary Pulmonary Coin Lesions

A REVIEW OF THE ENGLISH LITERATURE AND REPORT OF THIRTY-SIX CASES

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SINCE Graham and Singer[19] first showed that pneumonectomy was curative for lung carcinoma, and particularly since Alexander[4] called attention to circumscribed lesions of the lung, interest in the treatment of such lesions has become widespread. Adler[3] in 1912 emphasized the need for thoracotomy "with little hesitation" in dealing with suspected cancer of the lung. He must have been referring to small solitary lesions amenable to wedge resection because at that time lobectomy and pneumonectomy were far from accepted procedures.

Much has been written on pulmonary coin lesions and most such writings have emphasized the need for early thoracotomy to establish the diagnosis where other diagnostic methods have failed.[3–5,7,8,10–15,20–22,27–32,34–46,48] (A solitary or coin lesion of the lung is described as a rounded density as seen on x-ray which is 5 cm. or less in diameter.) In spite of the oft-reported high rate of maliguancy in these lesions, one may still frequently observe a "wait and see" attitude on the part of general practitioners and radiologists.[42] In fact, one not uncommonly hears of a family doctor advising against thoracotomy for these lesions.[2]

Many writers have stated that cancer of the lung, as well as cancer of any other site, must begin as a very small lesion. We subscribe to this principle. (Figs. 1 to 3.) It then follows that such small lesions should deserve the utmost concern of the medical profession and that a definite, aggressive plan of action be undertaken once they have been discovered.

There are many diagnostic tests which may be carried out prior to thoracotomy. These include bronchoscopy, bronchial and gastric washings, sputum studies, supraclavicular node biopsy, skin testing and so forth. In our hands these tests have never led to a prethoracotomy diagnosis in dealing with a coin lesion. We have therefore given them up, except for the skin tests, as being a further delay in the ultimate thoracotomy to which the patient must come, barring contraindications to operation.

Some investigators have held that the presence of calcification in a coin lesion indicates non-malignancy[1,2,9,16,23,24] and they do not advise thoracotomy. London and Winter[28] have described a case of a fifty-five year old white man with a calcified coin lesion which at thoracotomy proved to be primary adenocarcinoma of the lung. These authors suggest that primary adenocarcinoma of the lung may produce calcium apparently as a result of the function of the tumor itself. Storey et al.[40] reported a similar case. Tuttle[45] resected a calcified carcinoma of the lung.

At the Eighth Pembine Therapy Conference in 1951[37] it was stated that the presence of calcification in coin lesions is no absolute measure of benignancy and that these lesions should be resected.

Still others claim that calcium is indicative only of necrosis sometime in the past[47] and that its presence in a lesion does not indicate a benign lesion.[31,37,39,40,42,45]

Some writers describe the degree of density of calcium in a lesion as an important factor in determining malignancy.[47] Others claim that if a calcified lesion shows areas of non-calcifica-

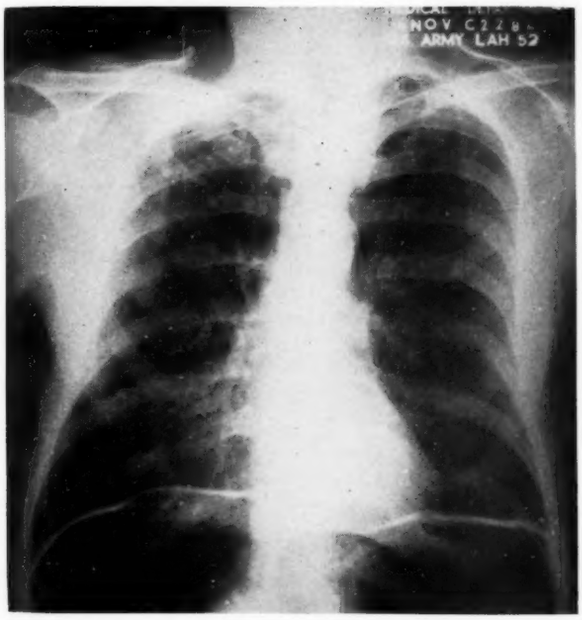

FIG. 1. X-ray of a fifty-four year old white man with active tuberculosis, right apex, undergoing treatment for his disease with pneumoperitoneum. In November, 1952, the small lesion in the mid-lung field overlying the third rib anteriorly on the left is barely visible.

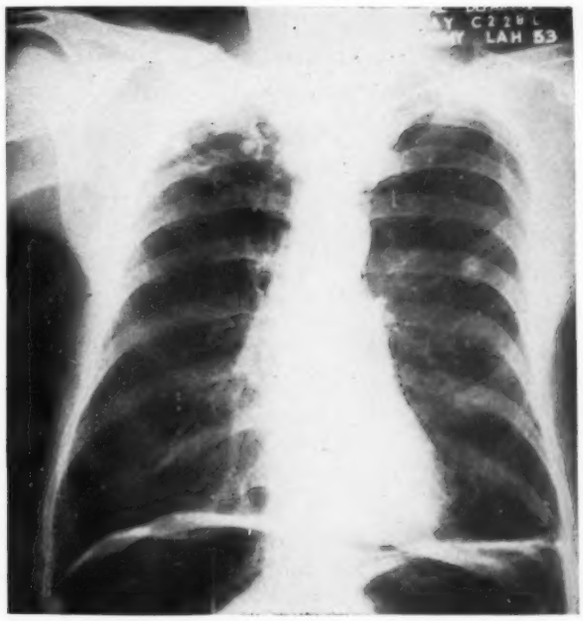

FIG. 2. Same patient, still undergoing pneumoperitoneum treatment for his acid-fast infection. The lesion in the left mid-lung field at this time (May, 1953) is somewhat larger than in Figure 1.

tion within it, it is an indication of breakdown and necrosis in the lesion, and they advise immediate thoracotomy to prevent a spread.[31]

Mathers[30] reported on eighteen patients with twenty-three tuberculomas which he followed up. The course of these lesions was: calcified, four; no change, seven; enlarged, five; cavitated, four; cavitated with spread, 3 (13 per cent).

Some authors have reported unfavorable development in benign calcified coin lesions.[6,31,40] Bugden[8] states that benign tumors may hemorrhage and suppurate. There are numerous reports in the literature describing breakdown and unfavorable development of non-calcified coin lesions and/or "tuberculomas."[9,13,24–26,29–31,33,37,40] Most of these reports advocate thoracotomy for these lesions.

It is our personal belief that calcium within a coin lesion *probably* means we are dealing with a benign lesion. We think that such lesions should be removed, however, because of the danger of unfavorable progression, cavitation, breakdown with spread, hemorrhage and the chance of malignancy being present.

All are agreed that in the non-calcified solitary lesion of the lung preoperative diagnosis is usually impossible and that an elaborate preoperative work-up is time-consuming, expensive and detrimental to the patient's

FIG. 3. Same patient as Figure 2. X-ray taken a year and a half after previous one. The lesion has progressed to substantial size. Despite the known presence of this lesion for over two years, at operation this proved to be a completely resectable epidermoid carcinoma.

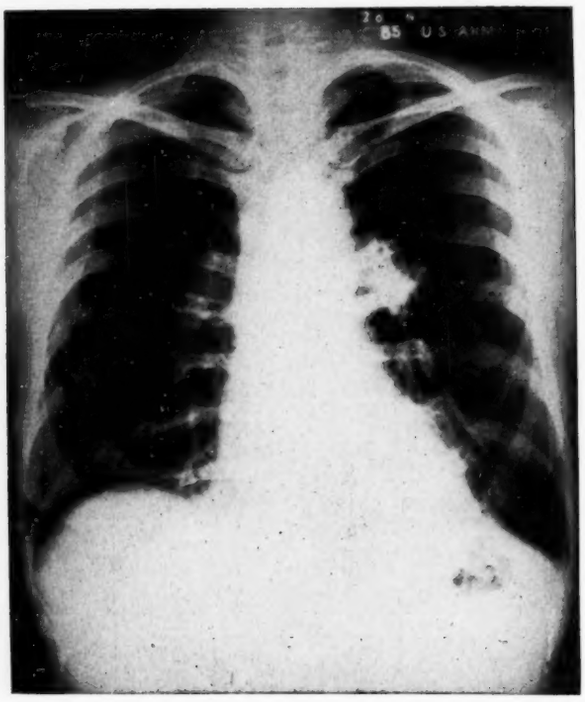

FIG. 4. X-ray of a fifty-three year old white woman. Postero-anterior projection shows calcification and slight hilar enlargement on the left.

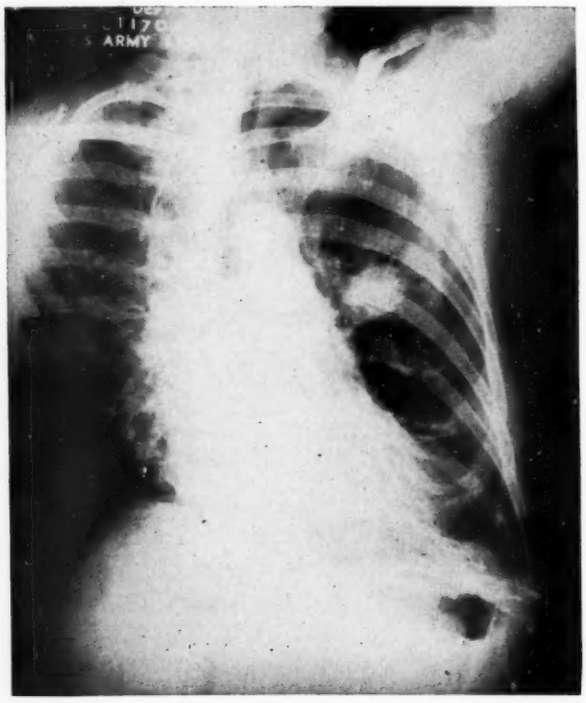

FIG. 5. Same patient. The oblique view clearly demonstrates the solitary lesion in the left mid-lung field. This proved to be adenocarcinoma which was thought to have been completely removed at surgery. There was no hilar involvement.

welfare.[2–5,7,9–12,15–18,21,26–28,32,34,37,38,40–45,48] We were unable to find any recommendation in this review of the literature advocating a "wait and see" attitude on undiagnosed non-calcified solitary lesions of the lung.

Our series comprises thirty-six patients, of which four were found to have carcinoma—an incidence of 11.1 per cent. Our rate of malignancy is not as high as in other reported series because in the military service we are dealing with patients in a younger age group. The patients' ages in this series varied from eighteen to sixty-seven.

The following illustrates the various pathologic diagnoses: carcinoma (three squamous, one adenocarcinoma), four; coccidioidomycosis, seven; hamartoma, three; tuberculoma, five; non-specific granuloma, ten; focal pneumonitis, seven.

Skin tests for tuberculosis, coccidioidomycosis and histoplasmosis were carried out on all patients preoperatively and in no case were the results of these tests at variance with the pathologic diagnosis (i.e., in no case was there a pathologic diagnosis of tuberculoma in the face of a negative P.P.D. skin test or vice versa).

Most of these lesions were picked up on routine x-ray of the chest, the patients having been without symptoms. The woman with adenocarcinoma had had two episodes of hemoptysis. (Figs. 4 and 5.) The three other cases of carcinoma, all of the epidermoid type

TABLE 1

Authors	Patients Coming to Thoracotomy	Malignancy	Per cent
Abeles and Ehrlich[2]	21	7	33⅓
Davis and Klepser[10]	67	37	55
Davis, Katz and Peabody[11]	67	34	50.7
Sharp and Kinsella[39]	55	15	27
Efller, Blades and Marks[15]	24	4	16.6
Grow, Bradford and Mahon[20]	86	20	23.2
French et al.	36	4	11.1
Totals	356	121	34

and in men, started as small isolated lesions. The patient shown in Figures 1, 2 and 3 was being treated in 1952 for tuberculosis of the right lung when a small lesion of the left lung was noted on x-ray. This was presumed to be tuberculoma and the patient was watched for

over two years before coming to surgery, at which time carcinoma was discovered.

We have combined our series with some others in the literature. The malignancy rate is 34 per cent for the total of 356 cases. (Table 1.)

SUMMARY AND CONCLUSIONS

1. Thirty-six cases of pulmonary coin lesions are presented. All patients were subjected to thoracotomy.

2. Four cases proved to be malignant—an incidence of 11.1 per cent, which is much lower than the incidence reported in other series.

3. All undiagnosed non-calcified solitary or coin lesions of the lung should be submitted to early thoracotomy. Preoperative diagnosis in these cases is difficult if not impossible.

4. The majority of calcified coin lesions should also be removed because of the danger of future cavitation, necrosis, breakdown and spread as well as hemorrhage and possible malignancy.

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DISCUSSION

Roy Cohn (San Francisco, Calif.): No one can disagree with the statement that small round lesions in the lung of the asymptomatic patient cannot be positively labeled except by excision; and no one can disagree with the fact that these lesions are frequently malignant, especially in patients over forty years of age. For these reasons the prevailing opinion in the surgical literature has been that early surgery is indicated. Along these lines lies the method by which we can improve the discouragingly low percentage of five-year arrest in cancer of the lung.

Radiologic and Public Health experts look upon this problem somewhat differently. Garland, in reviewing the experience of the mass x-ray experiment in Los Angeles where 1,867,201 persons had chest x-ray, concluded that aside from costing about $10,000 for each proved case of lung cancer, mass chest survey of the general population for the detection of cancer is not a useful or effective weapon.

Churchill, analyzing the results of the study of half the population of San Diego County by 70 mm. chest films, found that twenty positive cases of cancer were discovered. Follow-up of these patients showed an average length of life of nine months after the discovery of the disease. None of these patients were alleged to have no symptoms or symptoms of less than three weeks' duration. In addition, twenty-four patients died from carcinoma of the lung who were said to have had negative films on an average of sixteen months previously. Many similar reports can be found in the literature. On the other hand, there are an increasing number of case reports of round shadows in the lung that have been followed up for many years before removal showed them to be malignancies.

It would certainly appear that carcinoma of the lung behaves as Dr. MacDonald has emphasized for carcinoma of the breast, in that the important fact is the biologic relationship between the tumor and the host, and that a few weeks' time one way or another before definitive therapy is begun is not too important.

John F. Higginson (Portland, Ore.): A few years ago Dr. David Hinshaw collected cases of coin lesion at the Veterans' Hospital in Portland, and to those twenty-eight cases we had seen, eleven patients were added from my own private practice.

We reported these cases in the *Journal of the American Medical Association*, April 30, 1955, and established at that time the criteria which have been gone over by the essayist. The definition of a coin lesion is important because it is a term that has in the past connoted in many minds a sense of security and benignancy because it came down to us through the years as a radiologic term descriptive of its appearance on a chest x-ray. We are "stuck" with the term but it needs definition and we established these criteria for the consideration of coin lesions.

You must divorce this term from the term "solitary lesion" which appears in the literature also, for the simple reason that "solitary" gives you a wide play in the type and size of lesion that will be found. "Coin" lesion automatically implies the "trap" type of lesion, the kind which will cause trouble if left alone. I am emphasizing this as the essayist did, because I believe it is quite important.

In our series of thirty-nine cases there was an incidence of bronchogenic carcinoma of 10.3 per cent. I was quite interested to note this correlates almost exactly.

There was an over-all incidence of 15.5 per cent of malignancy, so coin lesions are significant. There is absolutely no way of knowing what these are until the pathologist gives his decision.

We can argue about other lesions and say that removal is or is not necessary, but there is no gainsaying the fact that a significant percentage of

these coin lesions are malignant and can be so determined only by removal.

LYMAN A. BREWER, III (Los Angeles, Calif.): This subject is one in which we have been keenly interested for a long time. Actually, as time goes on, more and more of these lesions will be discovered as the concept becomes more widely accepted that roentgenogram of the chest is an essential part of a general physical examination. Those who believe that routine x-ray of the chest is an expensive way to detect cancer miss the important point that many other pathologic conditions are also discovered. The diagnosis and treatment of these lesions, in addition to cancer therapy, as the authors have shown, make the routine chest film most valuable. It should be of interest to the surgeons at this meeting personally because physicians by and large have more routine x-rays than any other single group and some of us may be faced with the personal problem of deciding what to do with a small lesion seen on a routine film, as well as those concerned in our practice.

Our experience is similar to that of the authors. Certainly the question is raised by persons reporting a very high percentage of carcinoma in the coin lesions discovered on x-ray that only the obvious cases of carcinoma are coming to surgery. Therefore not only may some cases of cancer be missed but also certain benign lesions that are best treated by surgical removal.

In a series of approximately 500 cases of bronchogenic carcinoma we have been able to resect the malignant tumor in only 180 instances, or 36 per cent of this series. Thus in 64 per cent of the cases not even palliative resection could be carried out by the time the diagnosis was made. It is of interest in this group of patients that there have been seventeen instances of a solitary mid-lung carcinoma in which no symptoms were present. The asymptomatic mid-lung group of bronchogenic carcinoma is the group in which we have had our best early results. We believe the long-term results, too, are going to be much better than those published for symptomatic cancer. Actually, only three of the seventeen patients have died, one in one year and one in two years. The remainder of the patients are alive from one to seven years. There is no question that this is a big improvement over the results in the symptomatic group and it is reasonable to assume, as more and more of these cases are detected and resection is performed, that the general results of bronchogenic carcinoma will improve.

It was generally believed at one time that all bronchogenic carcinoma was visible through the bronchoscope. Our recent studies indicate that only 20 per cent of cancer of the lung can be seen at bronchoscopy. This leaves four-fifths of the lesions developing in the lung fields where they will cast a shadow early. Since the first patient to undergo pneumonectomy, performed in 1933, is still alive and is apparently cured, we know that as long as cancer is confined to the lung, cure is possible by pneumonectomy. Maybe we will find as time goes on that the predetermination of the growth habits of any given bronchogenic carcinoma is the most important factor in the cure rate. Perhaps we will have better tests to determine the existence of cancer itself, the gross pattern and the presence of metastases. However, until these factors are fully understood, further improvement in the results in cancer therapy are going to be along the lines pointed out by the authors. Calcium deposits in a lesion once thought to be a pathognomonic sign of a chronic infectious granuloma cannot rule out bronchogenic carcinoma or even benign tumor. We have had one case of bronchogenic carcinoma and two benign tumors with definite calcium deposits within the confines of the tumor. In a number of other cases there have been calcium deposits in the hilae and other parts of the lung adjacent to the developing bronchogenic carcinoma. Thus a calcium deposit in a possible carcinoma does not rule out the presence of a neoplasm. The physician must then redouble his efforts with tests, special films, etc., and exploratory thoracotomy when cancer cannot be completely ruled out. Furthermore, many cases of bronchogenic carcinoma do not show the tiny indentation described as being diagnostic of early cancer of the lung. These shadows may be round or smooth, as well as show irregular contours. Actually, most often in the mid-lung lesion the diagnosis can be made only by open thoracotomy.

With this aggressive policy of resecting these round lesions being pursued, what about the benign conditions which undergo resection? We support the authors' contention that granulomas of the lung, benign tumors and chronic abscesses which make up the vast majority of the benign lesions simulating broncogenic carcinoma are best treated with excision. This is a most interesting by-product of the cancer eradication program. What started out to be mainly a cancer detection and excision program has now proved most valuable for the identification and removal of these potentially serious benign lesions. Thus in reviewing any series of cases in which the number of malignant lesions has not been large one must always remember the tremendous value of resection of these potentially dangerous benign lesions.

I have enjoyed this article by Col. French and his co-workers, and wish to thank them for bringing this important matter so forcefully to our attention.

JOHN K. POPPE (Portland, Ore.): I, also, would like to commend the authors on an excellent presentation, particularly on their advice about not wasting time with extensive diagnostic procedures,

particularly bronchoscopy. My experience is that bronchoscopy does much more harm than good for peripheral coin lesions. It is almost invariably negative and gives the patient a false sense of security which sometimes delays excision six months, a year or longer.

The only exception I would make to the article is that I would be inclined also to abandon the skin tests which in my experience have been equally erroneous in arriving at an absolutely correct diagnosis. They tend to throw "red herrings" into the field and do not necessarily prove that the lesion is what that skin test shows.

Ross Robertson (Vancouver, B. C.): This article has interested me keenly and I think when we consider the question of carcinoma of the lung we must realize that it is the most common site of carcinoma in man. Many physicians believe that it is useless to diagnose carcinoma of the lung early since there is so little to offer the patient in the way of treatment; and as one of the discussers has pointed out, survey x-rays often fail to pick up cases sufficiently early to permit surgical treatment.

I would like to point out that these conclusions are not justified. Regarding the value of survey x-rays, it must be pointed out that a survey x-ray is quite different from periodic x-rays. Survey x-rays may pick up something that has been in existence for two or three years, whereas periodic x-rays every six months will reveal early lesions.

Concerning the results of surgical treatment for early cases of carcinoma of the lung, we have followed up sixty-six patients, who have undergone resections for bronchogenic carcinoma, for three years or more. In twenty-nine of these patients there was no lymph node involvement. Sixty-two per cent of these twenty-nine patients showed no evidence of carcinoma at the end of three years. A large number of these cases had been diagnosed by periodic chest x-rays. Consequently, when the lesion is diagnosed early, the patient has a fifty-fifty chance of survival.

M. A. Pfotenhauer (closing): The incidence of carcinoma at 10 per cent was interesting for us to hear since we believed that our series was quite low as compared to those in the literature.

An Unusual Biliary Obstructive Syndrome

JOHN P. TROMMALD, M.D., *Portland, Oregon*

THE symptoms and signs of acute cholecystitis are usually clear-cut. In diagnosing chronic cholecystitis there is always time for a thorough case study. When calculi are present the problem is most often not a difficult one. It is non-calculous disease of the extrahepatic biliary tract which throughout the history of medicine has been a source of controversy from the viewpoint of diagnosis and therapy. Oral cholangiography has been helpful, and more recently intravenous cholangiography has contributed additional information in certain cases. However, a good history is still by far the most essential diagnostic factor. This must not be ignored when symptoms persist or recur in spite of normal x-ray and laboratory findings.

The purpose of this paper is to review the significant features of three cases with history and physical findings typical of extrahepatic biliary obstruction, all having normal oral cholecystograms. Unfortunately intravenous cholangiography was not available when these cases were studied.

All the patients had similar pain, in the right upper quadrant or mid-epigastrium, frequently radiating through to the right subscapular region. This pain was intermittent, often severe and lasted from a few minutes to several hours, usually appearing after a meal. The total durations were one, two and four years, and in all the pain was disabling to the point that a state of near invalidism had been reached. Nausea and vomiting occurred, but not as frequently as the pain which came every day or two, sometimes as a heavy dull ache in the mid-epigastrium, sometimes as an excruciating, squeezing biliary colic. Loss of weight was another common feature, so much so that in the two older patients pancreatic malignancy was seriously considered. It was not a true anorexia, but rather fear of pain that kept these patients from taking adequate nourishment.

Examination showed tenderness over the area of the gallbladder or mid-epigastrium, or both. No masses were palpated. No clinical jaundice was present nor was the icterus index elevated. Liver function tests were carried out in one patient and gave normal results.

Oral cholecystograms and upper gastrointestinal x-ray studies were normal in all three patients. Pyelograms taken of two of the patients were negative. Unfortunately, no special effort was made to visualize the common duct. In the future we plan to take advantage of intravenous cholangiography in cases of this type now that it is available.

Surgery was recommended only after a fair trial of medical treatment, consisting mainly of antispasmodics and dietary management. No reasonable relief was thus obtained, and all of these patients pressed for an operation because of the severity and chronicity of their pain and its concomitant disability. The possibility of psychoneurosis had been considered in two of these patients, and certainly such patients can and do appear psychoneurotic and the evaluation of their pain is sometimes quite difficult.

At operation the common duct in all three patients was definitely dilated to 8 or 9 mm. Several enlarged lymph nodes along the common duct were found in two patients. In all three the gallbladder was slightly more opaque than normal due to a minimal thickening, but was freely compressible and without stones. The liver and pancreas were normal in appearance and to palpation, and there was no evidence of gastric or duodenal ulcer.

Because of inability to pass a 3 mm. Bakes dilator through the sphincter, duodenotomy was carried out. In one patient a pinpoint, markedly fibrotic papilla was encountered; in the other two only moderate narrowing and fibrosis were noted. In all three the fibrotic ring was transected, allowing dilatation up to 1 cm. Routine exploration revealed no common duct stones. The gallbladder was then removed

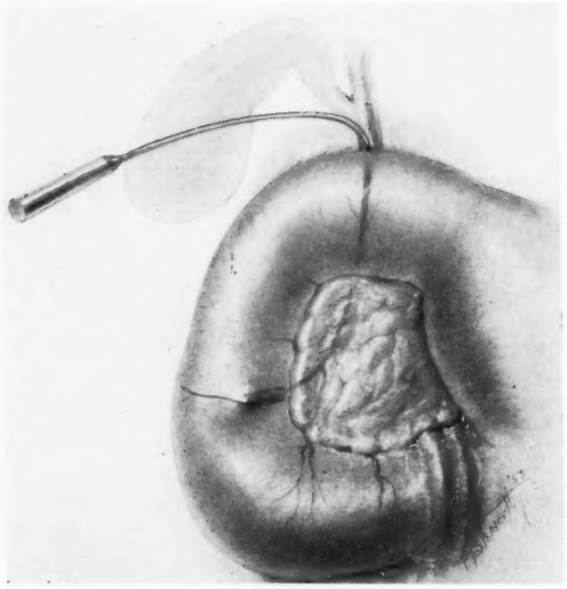

FIG. 1. Bakes dilator pressing stenosed papilla forward against anterior duodenal wall. This marks center of small transverse incision to be made in anterior wall. Duodenum should be modilized laterally when necessary.

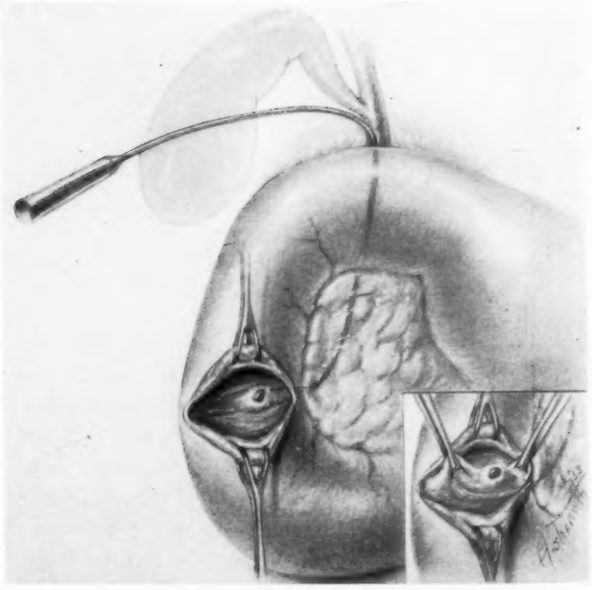

FIG. 2. Note presenting tip of Bakes dilator. Insert shows most important step of operation, the grasping of posterior duodenal wall with an Allis forcep on each side of papilla.

after insertion of a loose fitting, long-limbed T-tube and closure of the duodenotomy incision. The gallbladders were reported by the pathologist as showing "chronic cholecystitis." It is well to remember that in any large series of postmortem examinations at least 60 to 75 per cent of gallbladders examined are the site of some pathologic change.[1] Judd quite aptly stated that no one actually knew what constituted "chronic cholecystitis" either from the standpoint of clinical symptoms or from that of pathologic findings.[1] A biopsy specimen taken from the pinpoint sphincter showed marked fibrosis.

To date, two of the patients, a sixty-five year old housewife and a forty-three year old logger, have had complete relief from their pain and each has gained back the 20 pounds lost prior to surgery. It is well over two years since their operations. The third patient, a twenty-three year old housewife, has been entirely symptom-free except for two attacks of pain; the first lasted twenty hours and the more recent, three hours. All three patients believe that the surgery has been well worth while.

TECHNIC OF TRANSDUODENAL SPHINCTEROTOYM AND REVIEW OF OPERATIVE EXPERIENCES

Figures 1, 2 and 3 demonstrate points to be kept in mind during transduodenal sphincterotomy. The most important step in our experience is to secure firm hold of the posterior duodenal wall with an Allis clamp on each side of the papilla before the dilator is forced through. In this way the papilla is under control at all times and the whole procedure can be performed with ease through a small transverse incision in the anterior duodenal wall without undue trauma to the delicate edges of the duodenotomy incision.

In the past ten years I have performed twenty-one sphincterotomies in twenty patients, the average age being fifty-four years. Eighteen had definite fibrosis, and fourteen of these had calculous disease. The common duct has been dilated in all these patients except one where it was considerably thickened. Common duct stones were noted in three patients, two of whom had jaundice. The only other patient with jaundice, our first and most severe case of fibrosis, was operated on ten years ago. There were no stones in the gallbladder which was markedly shrunken and thickened, nor were there any stones in the common duct. There was complete ampullary obstruction and deep jaundice, and the liver showed gross evidence of damage. His health since sphincterotomy has remained excellent to date.

Fibrosis has been suspected when a 3 mm.

Bakes dilator could not be passed through the sphincter of Oddi from above. We have more recently come to believe that fibrosis should be considered when a 4 mm. dilator meets persistent unyielding resistance at the sphincter. Duodenotomy is carried out in all such cases, the papilla visualized and sphincterotomy performed when fibrosis exists.

Eleven short-limbed and ten long-limbed T-tubes have been used with equally good results, most of them having been removed at the end of the second or third week. There has been no suturing in the ampullary region except in one patient in whom a false passage was made while trying to force a 3 mm. sound under direct vision. Here it was necessary to repair the lacerated ampullary and common duct walls. In such circumstances we believe the use of a long-limbed tube is advisable, and leave it in for two or three months. Whenever such a tube has been used we have been careful to see that its diameter is 3 or 4 mm. less than that of the common duct and ampulla, giving a loose fit so that the opening of the pancreatic duct would not be obstructed. Mahorner recommends fenestrating the portion of the tube running through the common duct. Cattell[2] believes that a snug-fitting tube is all right, and in his extensive experience has not thought that the pancreatic duct opening was ever thus obstructed. There has been no flare up of pancreatitis in any of our patients.

Three duodenal fistulas occurred, all appearing the sixth or seventh day. They healed spontaneously, two of them in a week with only slight drainage, the third being quite serious and persisting for two months with copious drainage. In the third patient, a serious case, a short-limbed T-tube had been used. Should a duodenal fistula occur we cannot help but believe that one is better off when a long-limbed T-tube has been used, and healing should be quicker. We have been equally satisfied with short- and long-limbed T-tubes in most cases, but would favor the use of the long-limbed T-tube when there has been undue trauma in the ampullary region necessitating sutures, or when duodenal closure has been unsatisfactory or difficult due to injury of the duodenal wall.

One postoperative hemorrhage into the bowel occurred on the first postoperative day. This must have been from the sphincterotomy site or the duodenotomy incision. It subsided spontaneously after a loss of approximately 1,500 cc of blood.

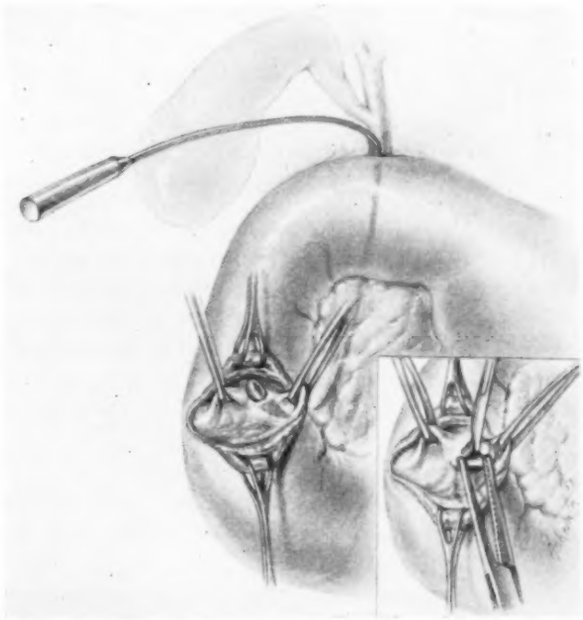

FIG. 3. Bakes dilator is forced through fibrotic sphincter and (insert) is followed back with straight hemostat. Its jaws are then spread and fibrotic sphincter incised its full length while held on stretch, making certain to cut through all the fibrotic area in superior lip of papilla.

There have been no deaths, and good results have been obtained in all of the cases we have been able to follow (eighteen of the twenty) except one. In this patient sphincterotomy was repeated because of recurring symptoms, and he has been well since the second operation four years ago. Either the fibrotic area had been incompletely incised or fibrosis had recurred.

The gallbladder should always be removed after sphincterotomy, regardless of its condition, inasmuch as it ceases to function.[3] We know of two cases in which this was not done and cholecystectomy was later necessary to relieve troublesome symptoms. Animal experiments[3] and clinical experience[4] have proved that a properly incised sphincter remains incompetent and retracted with or without a long-limbed T-tube. Postoperative choledochograms have been taken two weeks following surgery in patients in whom the short-limbed tubes have been used and have shown normal-sized ducts with rapid emptying. It is our plan to carry out cholegrafin studies in the patients who have had sphincterotomy over two years ago.

Anyone wishing to review the subject of sphincterotomy should refer to the papers of Strode,[5] Cattell and Colcock,[6] Doubilet and Mulholland,[3,7] Mahorner and Browne,[8,9] and Partington.[10]

COMMENTS

Ogilvie[11] recently wrote an article advising any young surgeon who would keep the respect of his students, the trust of his colleagues and the integrity of his conscience to deny the existence of non-calculous gallbladder disease and chronic appendicitis, or at least to refuse a fee for operating on them. "Only in middle life when he has set his reputation in an unassailable position by years of honest dealing may he admit to himself that such lesions do exist, and recommend to patients that they be treated by operation."

This was also the teaching during our medical school and postgraduate years and certainly the burden of the proof is on the surgeon who removes numerous functioning non-calculous gallbladders and fails to obtain symptomatic relief for the patient.

In our total surgical experience we have removed six non-calculous gallbladders, two of them in secondary operations following cholecystostomy for empyema without calculi, the three reported here, and one in which persistent spasm of the sphincter was thought to be present. Sphincterotomy was considered necessary in the four non-acute cases. All have been relieved of their symptoms for two years or more.

It is our intent to continue a conservative policy towards non-calculous gallbladder disease. Nevertheless, there are patients much like the three reported herein who drift from one physician to another without relief because too little attention is paid to their complaints and too much to their negative x-ray and laboratory findings. Partington[10] reported three very similar cases in 1952, but was able to give excellent preoperative radiographic evidence of a dilated common duct and fibrotic terminal common duct in each instance.

Cattell and Colcock[6] reported only seventeen patients as having appreciable common duct dilatation of forty-nine in whom fibrosis of the sphincter of Oddi was demonstrated. Therefore, this condition must be considered even when a normally sized common duct can be radiographically demonstrated, so long as there is a good history and a careful differential diagnosis has been accomplished. In our own series a dilated common duct has been present in seventeen of eighteen cases of proved fibrosis.

In 1933 Strauss[12] reported an interesting series of cases with chronic biliary stasis. He suggested that the fibrosis encountered in cases similar to ours had as its pathologic basis an infection which begins as a duodenitis and ascends the common duct and also the pancreatic duct in the 90 per cent having a "common channel." "These cases all have as the pathological basis of their symptoms an infiltrative inflammatory process of the lower portion of the common duct, with thickening and narrowing of the ampulla of Vater." We are inclined to agree with this except that spasm and inflammation without actual infection may well be the trigger mechanism which sets off the ampullary involvement. Just when spasm or so-called hypertonic dyssynergia[13] enters the picture is difficult to ascertain, but certainly it must play a definite part. The end result of this type of ampullary obstruction can result in liver and pancreatic damage if unrelieved.

SUMMARY AND CONCLUSION

Three cases have been reported with symptoms typical of extrahepatic biliary obstruction and having normal oral cholecystograms. At operation all had dilated common ducts and either a marked or incipient fibrosis of the sphincter of Oddi without calculi. All have been relieved for two years or more by transduodenal sphincterotomy and cholecystectomy. A discussion of our experience with transduodenal sphincterotomy has been given. There may be a small number of cases encountered in any series brought to surgery for biliary disease in which the history, regardless of negative x-ray and laboratory findings, has made operation mandatory. The many reported surgical failures (well over 50 per cent) following cholecystectomy in non-calculous biliary tract disease are usually described as having the postcholecystectomy syndrome. As a rule these failures are due to either incorrect diagnosis or inadequate surgery, and do not represent a true syndrome.

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DISCUSSION

DEAN B. SEABROOK (Portland, Ore.): I think Dr. Trommald's approach to these cases is courageous and very fortunate since the results were excellent. Nothing succeeds like success. However, even though I am convinced sphincterotomy is an excellent procedure, unless the surgeon is extremely careful in selecting his cases, many unnecessary and even harmful operations of this type may be performed.

I am very sure that Dr. Trommald is careful in selecting his cases. I am familiar with nearly all the operations he has performed and they have been most satisfactory; as a matter of fact, so have mine.

Sphincterotomy, although not always successful, may be found useful in the following conditions: (1) cholangitis, (2) fibrosis of the sphincter (localized cholangitis), (3) pancreatic stones, (4) chronic and recurrent pancreatitis, (5) early biliary cirrhosis, (6) recurrent common duct stones, and (7) any condition in which prolonged T-tube drainage is deemed advisable.

Good results will be obtained if these indications are present; the sphincter is properly cut, at least 1 cm. through the anterior border; no stitches are used, because the pancreatic duct may thus be obstructed; and the long T-tube is not used, again because of danger of obstructing the pancreatic duct. Neither Dr. Trommald nor I have had pancreatitis follow in our small series of cases.

The newest operation of cutting the pancreatic tail and anastomosing it to the jejunum seems to be getting favorable comment. In approximately 36 per cent of the cases there is a communication between the ducts of Wirsung and Santorini. Theoretically, these patients should not have pancreatitis as a result of obstruction to either the ampulla or the pancreatic duct beyond this union. I can visualize an obstruction of the pancreatic duct proximal to the sphincter, but not at the sphincter which might be drained by anastomosing the tail. It seems to me, however, since sphincterotomy is simpler and safer, perhaps this should be done first and, should this fail, anastomosis of the tail then be tried.

Dr. Trommald's cases in other hands may well have followed a tragic course. Sooner or later, because of right upper quadrant pain, the patients would have had cholecystectomy. This would have been followed by more pain and distress, and a label of "postcholecystectomy syndrome" would be placed upon them. These patients would have drifted from doctor to doctor, miserable and misunderstood. Dr. Trommald's understanding of the basic pathology in these cases and his proper and efficient attack thereon, namely, cutting the fibrosed sphincters, has completely cured these patients.

LESTER R. CHAUNCEY (Portland, Ore.): I would like to comment upon one failure of the operation, a failure that was included, I believe, in Dr. Trommald's report.

The patient about whom I wish to comment was a woman in whom Dr. Trommald encouraged me to perform sphincterotomy. She had had typical symptoms, and a dilated common duct was found. There were no stones in the gallbladder and it seemed proper to perform sphincterotomy, which we did. The gallbladder was not removed. Three months later this had to be removed necessitated by the persistence of pain during those three months. I would like to stress the fact, therefore, that the gallbladder must be removed if sphincterotomy is performed. Just why this is so, I do not know. Perhaps Dr. Trommald would comment upon this in his closing remarks.

DAVID METHENY (Seattle, Wash.): I wish to report four cases of fibrosis or stricture of the ampulla of Vater, two patients with jaundice and two patients without.

The first patient was a man with gallstones, but no stones in the common duct. His common duct was slightly dilated. An operative cholangiogram showed the stricture, and transduodenal

sphincterotomy was performed. He has had no symptoms and remained well for three years.

The second patient was a man who had had his gallbladder removed for stones. At that time it was thought that the common duct was normal. Two years later he seemed to have a residual cystic duct syndrome. At operation the common duct was slightly dilated and contained no stones. The probe would not pass through into the duodenum. Sphincterotomy was performed and he has been well and without symptoms for six years.

In 1942, a twenty-one year old girl was operated upon by a general practitioner for what he thought was gallstones and stones in the common duct, as the patient had colic and jaundice. A gallbladder without stones was removed and the common duct was explored. No stones were found and a probe could not be passed into the duodenum. He placed a T-tube into the common duct, thinking there might be an inflammatory stricture, and continued T-tube drainage for about three months. At that time he removed the T-tube and within four hours the patient had another attack of colic followed by jaundice.

At exploration, I found that the common duct was slightly enlarged and it was not possible to pass a probe through the common duct into the duodenum. A transduodenal exposure of the ampulla was made and it was then possible to pass a small probe up into the common duct from below. The stricture was gradually dilated until it was possible to pass a T-tube through the stricture into the duodenum. This was kept in place for about fifteen months, and then removed. She has had no trouble since the T-tube was removed in 1943.

The fourth patient was a girl who had her appendix removed when she was twenty-two and her gallbladder drained at twenty-three. When she was thirty-six, her brother-in-law removed her gallbladder, which had no stones, and assured her that she would have no further trouble with her gallbladder system. When she was forty-two years old, I saw her; she was complaining of abdominal pain and what she called gallbladder colic. She stated that it was similar to the attacks that she had had before. On further study we found that she had porphyruria for which she was treated for two years. During this time she complained of recurrent attacks of moderate "gallbladder colic." Jaundice then developed. Exploration showed a dilated common duct, no stones, but fibrosis of the sphincter of Oddi, which was cut through transduodenal exploration. That was five years ago and she has had no gallbladder colic since. However, she still has porphyruria.

John R. Paxton (Glendale, Calif.): There are two comments I would like to make regarding this condition. First, the name with which this condition has pathologically been described is sclero-odditis of del Valle. About three or five years ago Dr. Berne kindly gave me the article on this subject, which had been translated by one of his residents from the South American literature.

Second, I operated upon two patients who had hypertrophy of the sphincter at the papilla. In the open duodenum I had difficulty finding the papilla, but by palpation I discovered that each had hypertrophy of the sphincter muscle, and on palpation it stood up about the size of a pea. In transecting this, the problem arises as to the dangers of subsequent strictures following sphincterotomy. These two cases convinced me of the unlikelihood of producing stricture following sphincterotomy if it is complete. By transecting the hypertrophied muscles, the muscle completely disappears by retraction. In cutting the sphincter muscle in the anus, when the fibers are completely transected, the circular muscles completely retract. Therefore, only fibrosis and no narrowing should be present.

In the two patients in whom complete transection was performed, the pea-sized mass which could previously be felt had completely disappeared.

Alfred Strauss (Chicago, Ill.): I am very much impressed with Dr. Trommald's paper on cutting the sphincter of Oddi from the duodenal side for drainage and doing away with obstruction and malfunction of the sphincter of Oddi. His cases show particularly that his method of cutting the sphincter seems to be very effective.

As Dr. Trommald mentioned in his paper, we reported fifty-six cases in 1933, and have had quite a large series since. In those early days we performed common duct drainage when there was definite inflammation of the common duct for a long period of time (six or eight weeks) and in many instances the patient was cured. However, in some of these patients in whom the sphincter of Oddi would not permit the proper drainage, we performed common duct duodenal anastomosis, but found that some patients regurgitated into the liver with marked symptoms of temperature and pain. We operated upon some of these patients by adding gastroenterostomy which reduced the interduodenal pressure. These patients were symptomless.

About ten years ago, we decided that the Roux-Y operation was simpler to do than common duct duodenal anastomosis and gastroenterostomy. However, now I will have to admit that all of these are more or less major operations compared to what Dr. Trommald introduces in a simple cutting of the sphincter of Oddi from the duodenal side which, in the cases reported, seems to be very effective and evidently does the work as well, if not better, than the Roux-Y or other major procedures we have performed in the past twenty-five or thirty years.

JOHN P. TROMMALD (closing): Dr. Seabrook's words mean a great deal since he has encouraged me at all times in developing this subject. We wrote a paper on fibrosis in 1949, at that time each reporting four cases.

Dr. Chauncey's case is one of the two mentioned in which the gallbladder was left at the time of sphincterotomy and had to be removed at a later date. Drs. Doubillet and Mulholland showed that the gallbladder no longer functions after sphincterotomy, and Dr. Chauncey's case gives ample clinical proof that cholecystectomy should be performed any time the sphincter is severed when the gallbladder is present.

Dr. Zeller's case* undoubtedly falls into the same group as the three presented, and divulsion of the sphincter was obviously adequate in this case. I believe that divulsion is satisfactory as long as the sphincter is completely defunctionalized, but if the resistance is great or if there is any doubt of even a few fibers remaining intact, incision under direct vision seems the better procedure. I have assisted at an operation during which an unrecognized false passage was made by undue forcing of a dilator. The patient died in forty-eight hours from retroperitoneal sepsis. If duodenotomy had been performed this would have been recognized and the fatality might well have been avoided.

Dr. Metheny's cases are most interesting, and the more of these we hear reported the more certain we become that this condition is perhaps not an uncommon one, but one which has been frequently overlooked and inadequately treated on a medical regimen.

Dr. Paxton's description of a bead-like hypertrophied sphincter was well demonstrated by a postoperative lipiodol choledochogram of my first patient operated upon ten years ago, showing complete obstruction at the papilla and marked biliary and pancreatic duct dilatation. Cholecystectomy and choledochostomy had been performed six weeks previously without relief. No stones were present, and at the second operation the duodenum was first opened and the bead-like papilla was visualized and incised with immediate gush of bile. There has been complete relief to date. This bead-like sphincter had been interpreted by the radiologist as a stone. The other type of deformity often seen is a narrowing of the terminal centimeter or so of the common duct as described by Dr. Metheny. This is also relieved by sphincterotomy.

It was particularly gratifying to have comments from Dr. Strauss since I quoted his most interesting paper published in 1933. His cases were quite similar to those discussed and it is my belief, as he stated in his discussion, that many of them could have been handled by sphincterotomy. He added gastroenterostomy to choledochoduodenostomy so as to avoid an ascending cholangitis. In none of my sphincterotomies has there been any cholangitis, probably due to the fact that the oblique course of the common duct through the wall of the duodenum acts as a valve. Incision of the sphincter without actual removal of any portion of it seems to have been adequate, although in several cases sections of sphincter tissue have been removed for biopsy.

* During this meeting, Dr. Zeller reported the case of a twenty-five year old woman with symptoms similar to those included in my article. He treated this patient by divulsion of the stenosed sphincter of Oddi without opening the duodenum by passing graduated sounds. The patient had complete relief, and Dr. Zeller brought up the question of whether divulsion was as satisfactory as cutting the sphincter.

The Combined Inguinoabdominal Repair of Inguinal Hernia

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THE cardinal principle in the repair of inguinal hernia is the complete obliteration of the sac and adequate repair of the transversalis fascia. It is accepted that in indirect inguinal hernia the sac should be excised; however, in the care of direct hernia it is frequently possible to obliterate the sac by invagination. The manner in which obliteration of the sac is obtained is unimportant as long as the proper end result is obtained.

Accurate statistical results of hernia repairs are extremely difficult to obtain and to evaluate. A higher incidence of recurrence is expected in direct or sliding hernia than in indirect hernia. Having labored under the concept that the majority of recurrences following surgery for inguinal hernia were of the direct type, a study of this problem was undertaken. Records were studied of all patients admitted to the Hospital of the Good Samaritan, Los Angeles, California, for the repair of recurrent inguinal hernia from the years 1950 through 1954. Surprisingly, results showed that (of 229 patients) 61 per cent had recurrent indirect inguinal hernia. Operative reports indicated that many of these had well formed and thickened indirect sacs, some of which extended throughout the length of the inguinal canal Additionally, of these indirect recurrences, twenty or 8.7 per cent were sliding hernias. Since the usual incidence of sliding hernia is accepted to be from 3 to 5 per cent, this figure suggests that the recurrence rate in sliding hernia is higher than appreciated.

Since 1935 one of us (G. K. S.) has used a combined inguinoabdominal incision for the repair of sliding hernia.[1] The La Roque[2] procedure can be performed expeditiously and without increasing morbidity and mortality rates. Experience gained with the technic suggested that it had more widespread application to the treatment of inguinal hernia than sliding hernia alone. The statement that laparotomy should never be performed in conjunction with an inguinal incision has been made by some (Ryan,[3] and Zimmerman and Anson[4]). Such a categorical statement should not go unchallenged. The combined inguinoabdominal procedure in properly selected cases insures better closure of the peritoneal defect, permitting accurate approximation of the supporting transversalis fascia from the inguinal side. Therefore it has been our custom to use this procedure in: (1) reucrrent indirect inguinal hernia with thin and friable sacs; (2) irreducible hernia alone or with strangulated portions of omentum or intestine. Intestine and/or omentum are withdrawn into the peritoneal cavity rather than being pushed blindly from below. This minimizes the possibility of trauma to irreducible elements and permits any necessary reparative procedures under direct vision. Gangrenous bowel can be removed through the inguinal route by placing one set of clamps on viable bowel in the peritoneal cavity and another set on viable bowel just below the internal ring. After dividing the bowel, the proximal ends can be covered with gauze and brought through the internal ring and out of the abdominal incision, permitting extraperitoneal anastomosis. Occasionally an irreducible hernia may spontaneously reduce itself under spinal anesthesia before the incision is made. In this situation the use of the combined inguinoabdominal incision permits inspection of the bowel and omentum, which is frequently difficult from the inguinal approach alone. (3) Femoral hernia can easily be

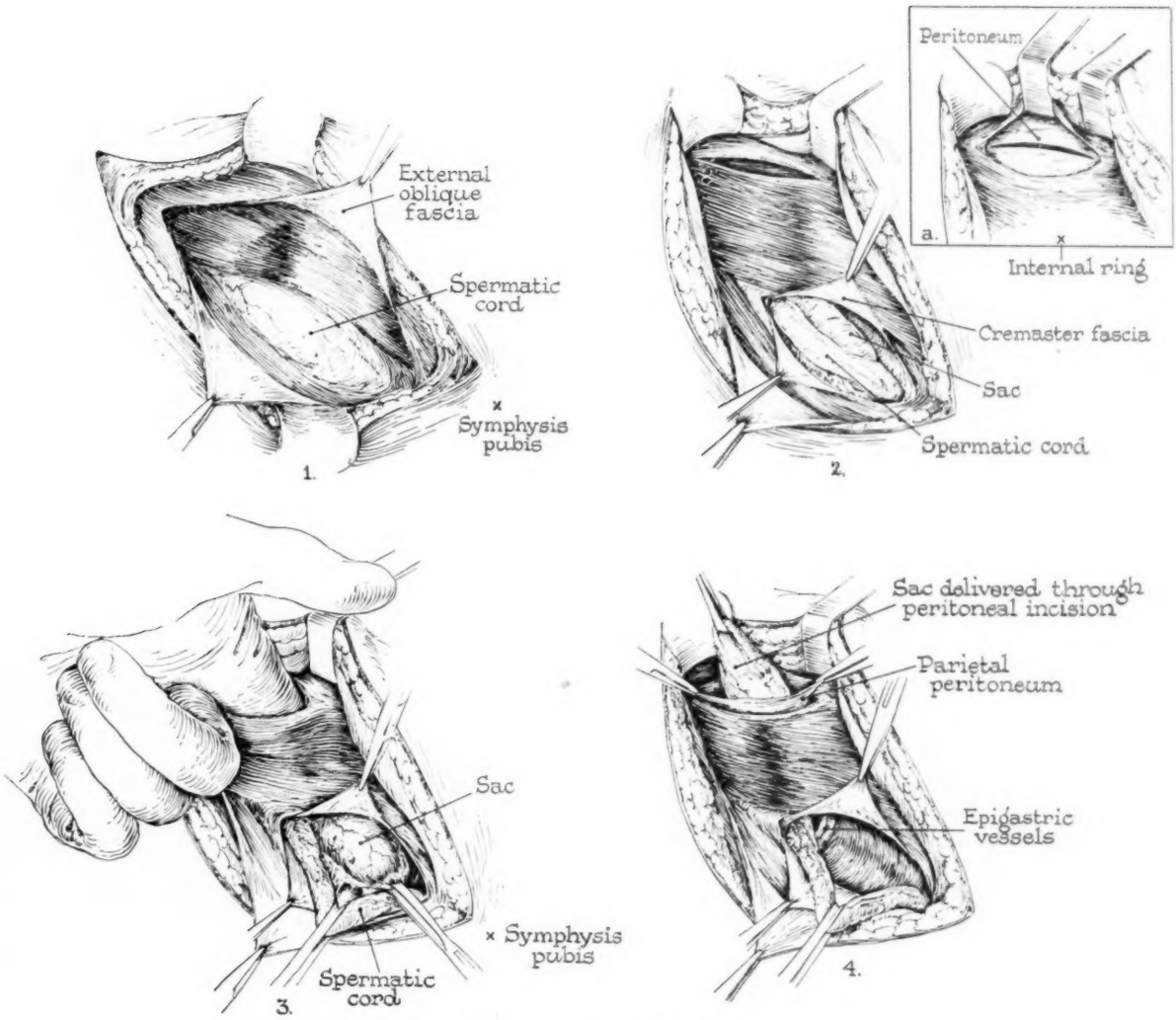

FIG. 1. Mode of delivery of indirect sac through combined incisions.

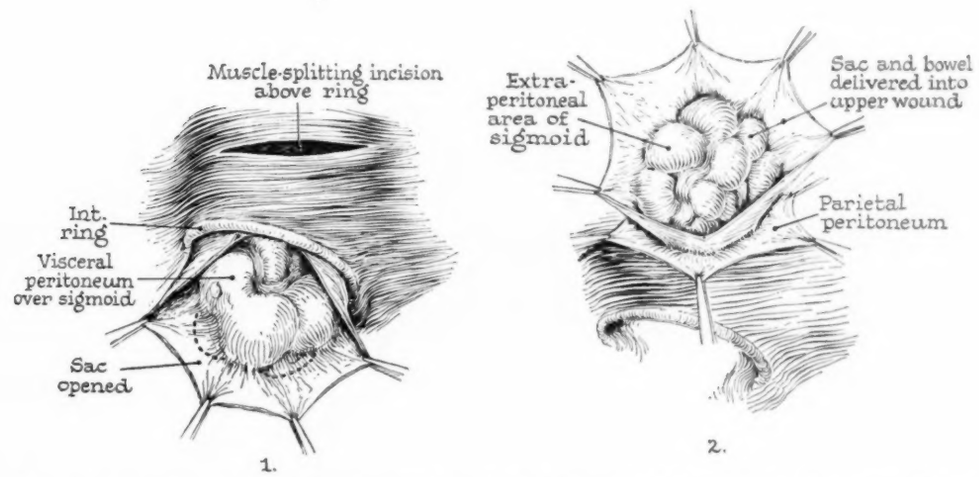

FIG. 2. Delivery of left sliding hernia through abdominal incision. Sac is then sutured over extraperitoneal sigmoid and replaced within abdomen.

handled from within the abdomen, particularly when irreducible elements are present. (4) Adherence of the sigmoid solon to the sac in a left indirect inguinal hernia is relatively common and constitutes a true sliding hernia. Attempts to dissect the sigmoid free from the sac through the inguinal approach make it difficult to close the peritoneal defect. Injury to the mesentery of the sigmoid is always a danger. It is therefore our opinion that this lesion is best treated with a combined inguinoabdominal approach.

The technic of performing this combined approach increases the operative time approximately ten to fifteen minutes. The skin incision is extended cephalad, as is the incision in the external oblique fascia. A muscle-splitting incision is then made at about the level of McBurney's point. The peritoneal cavity is opened. The abdominal defect is recognized from within and, with the finger in the sac from above, dissection from the inguinal side is facilitated. When bowel or omentum is entrapped in the sac, it is easily feed from the abdominal side and proper corrective measures can be taken. Following complete excision of the sac and its closure from within, the peritoneum and transversalis fascia of the McBurney incision are closed. The transversalis fascia overlying the internal ring is carefully closed from the inguinal side. The inguinal canal is then repaired in the manner which seems best indicated. (Figs. 1 and 2.)

Those of our residents who have become familiar with this combined approach in its extended application to inguinal hernia believe that they are more secure in the closure of the peritoneal defect than with the inguinal approach alone. It is our belief that the combined inguinoabdominal approach, properly applied in the treatment of inguinal hernia, will result in a lower incidence of recurrent indirect inguinal hernia. We do not concur with those authors who advocate intra-abdominal repair of inguinal hernia in all cases (Jacobsen[5] and La Roque[2]). The application of this technic to uncomplicated inguinal hernia is unwarranted.

CONCLUSIONS

The combined inguinoabdominal approach is applicable to the treatment of: (1) sliding inguinal hernia, (2) recurrent indirect inguinal hernia, (3) femoral hernia and (4) irreducible hernia. In over fifty cases there has been no increased morbidity and no mortality associated with this procedure. Such a high recurrence rate of indirect inguinal hernia, as found in this study, indicates that the customary method of treatment of the peritoneal defect from the inguinal approach alone is not completely satisfactory. The addition of the combined inguinoabdominal approach to the armamentarium of the surgeon is surgically sound.

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DISCUSSION

Charles E. MacMahon (Seattle, Wash.): I have enjoyed, now, on two occasions the brief and clearly defined contributions of Dr. Smith on the problem of inguinal hernias of varying types. The very fact that he has believed this subject important enough to present to this society gives me a very welcome sense of relaxation and relief. When in surgery performing those standard procedures indicated for the average patient's survival or comfort, I sometimes dream of the orlon-knit aorta, the patient with advanced mammary carcinoma being deprived of her pituitary, and that person with carcinoma of the stomach which did not respond as well as we hoped to radical gastric resection being further aided by having the right lobe of his liver bobbed with a liquid nitrogen knife. To realize in this dream, that somewhere in the world there is a surgeon who still has the courage in the age of the refrigerated patient to continue to try to improve the repair of that common affliction of mankind, a rupture, is indeed heartwarming. Since Dr. Smith's previous presentation on this subject for the society in 1950, he has kept me supplied from time to time with reprints which have been given to those of our surgical residents who seem capable of learning the basic principles of surgical technic required in the adequate and proper repair of the difficult sliding hernia. It was not until I had used the transabdominal approach in the repair of sliding hernia that I fully understood and clearly saw the anatomy of this problem. In my own experience a slight modification of this

technic applied to the femoral hernia has been most helpful. I am quite certain that the four criteria of selection for this approach as set up by Dr. Smith (namely, (1) the hernia with the thin friable sac, (2) the irreducible hernia, (3) the femoral hernia and (4) the true sliding hernia) can be improved only by amending to include the hernia with a wide neck sac, which with the more conventional approaches can be most difficult to close properly.

SUMNER EVERINGHAM (Oakland, Calif).: I would like to demonstrate a method that we have used for teaching the handling of sliding hernia to our interns and residents.

A paper bag could represent an opened hernial sac and an attached rolled towel the sigmoid or cecum extending well distally in the upper and lateral aspect. It is, of course, not feasible to strip the peritoneum from the contained viscus without jeopardizing the blood supply. However, if vertical incisions are carried down to the internal ring on either side of the large bowel, this can be inverted into the peritoneal cavity and closure carried out with a purse-string suture inserted from within the sac. This can be reinforced at a higher level for further security, and continued repair of the hernia can be performed as indicated.

In our hands this procedure has been quite adequate for handling the problem of sliding hernia, but I bring up this illustration more for the help it gives for instruction of students, interns and residents.

GORDON K. SMITH (closing): Dr. Everingham's illustration of a sliding hernia is quite ingenious. I have argued this point with Dr. Wise from Portland, who has sewn pieces of cloth together to demonstrate the mechanism in which a sliding hernia occurs. I fully appreciate the fact that many fine surgeons with wider experience than mine repair sliding hernias entirely from below. However, I believe, after using the combined inguino-abdominal approach, it has much wider application in the treatment of inguinal hernia than sliding hernia alone.

Duodenal Diverticula in Common Duct Disease

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It is usually stated that duodenal diverticula do not give rise to characteristic symptoms and that, in fact, they are quite harmless. Moreover, it has been said that when important clinical symptoms are associated with the presence of the diverticula, operation often reveals such conditions as an ulcer, gallstones or pancreatitis to explain the clinical picture. This viewpoint has been expressed by many observers and is undoubtedly correct in the majority of cases. However, we have seen six patients in whom biliary symptoms and pathologic changes appear to have been due to a perivaterian diverticulum. These cases form the basis of the present report.

REVIEW OF THE LITERATURE

Search of the recent literature yields a number of observations which are pertinent to the present problem. Cattell[6] reported an incidence of duodenal diverticula of 1.5 to 1.9 per cent on x-ray examination, and up to 14.5 per cent on autopsy studies. Pearse[13] stated that 75 per cent of diverticula of the duodenum are on the concave aspect of the descending portion of the duodenum. Benninghoven,[3] in 1931, demonstrated a diverticulum by x-ray, and at autopsy the common duct was found to empty into the diverticulum. Collett[7] reported a case in which the common duct entered the diverticulum as shown by cholangiography and upper gastrointestinal radiography. Blegen[4] also reported a case in which the common duct entered a diverticulum.

Despite the relatively common occurrence of diverticula in this vital area, experience has shown that they usually do not produce any interference with neighboring structures. However, several important observations have been recorded of perivaterian diverticula causing the syndrome of biliary obstruction. Picard and Hardy[15] reported the case of a patient with a dilated common duct without stones in either the gallbladder or common duct. The patient had complained of pain in the right upper quadrant with low grade fever and slight jaundice. Barium meal and cholangiography revealed the common duct to be compressed by a diverticulum. Behrend[2] reported the case of a fifty year old woman with abdominal pain of ten days' duration associated with slight jaundice; a diverticulum adjacent to the ampulla of Vater was seen by x-ray. At surgery the duct was compressed by the diverticulum and no gallstones were found. Delannoy and Tacquet[9] reported the case of a forty-seven year old woman who had recurrence of right upper quadrant pain followed by jaundice and fever five years after cholecystectomy for gallstones. X-rays revealed air in the biliary tree. At surgery a perivaterian diverticulum was found together with a dilated common duct, but again no gallstones were present. A fistula connected the common duct and diverticulum, and it was the author's belief that this fistula was due to ulceration of the diverticulum. Ogilvie[12] reported four cases seen at autopsy in which a diverticulum was found to be the cause of a dilated common duct or pancreatic duct, or both. In addition, all four of his cases had evidence of acute pancreatitis, which appeared in each instance to be the cause of death. Nicholson[11] recorded the case of a sixty-six year old man who complained of epigastric pain and jaundice. At autopsy a dilated common duct and cystic duct, plus an enormous gallbladder, were found. A peri-

vaterian diverticulum was firmly bound to the common duct with fibrous adhesions compressing it. Other isolated case reports are to be found in the literature.[1,16] Mahorner,[10] Chitambar,[8] Pearse[13] and Woodruff[17] discuss biliary and pancreatic disorders due to perivaterian diverticula, but do not cite cases of their own.

The following six cases of diverticula of the duodenum adjacent to the ampulla of Vater or lying along the common duct gave symptoms of and were associated with biliary tract disorders or pancreatic disease.

CASE REPORTS

CASE 1. L. B., a fifty-seven year old white woman, was first seen in October, 1953, with a history that in 1946 she had had cholecystectomy performed presumably for stones. Right upper quadrant pain had been present since that time, and had gradually become more severe and more disabling. A month before she had had an acute attack of right upper quadrant pain which she described as similar to her previous gallbladder colic. This was associated with nausea and some vomiting. Most of the pain had occurred twenty or thirty minutes after meals. Examination upon hospital entry revealed a moderately obese woman with no remarkable physical findings. The serum bilirubin was normal, the serum lipase moderately elevated and the gastrointestinal x-ray examination was negative. Her disability was thought to be due to chronic pancreatitis with common duct stone or stricture as additional possibilities.

On November 16, 1953, operation was performed. The gallbladder had been removed at a previous operation. The stomach, duodenum, common duct and pancreas were grossly normal. The common duct was opened and explored without finding stones or stricture; a T-tube was inserted for prolonged drainage. This resulted in a disappearance of pain, but when the tube was clamped pain was noted in the scapular region; this was relieved by opening the tube.

In April, 1954, cholangiograms and gastrointestinal series were done which demonstrated a duodenal diverticulum at or near the papilla of Vater. (Fig. 1.) On May 11th, the patient was reoperated upon with the T-tube in place. The duodenum was reflected medially and a diverticulum, 2½ cm. long with a neck 5 mm. across, was found on the posteromedial aspect of the duodenum close to the entrance of the common duct. The diverticulum was opened, and a separate opening in the duodenum was made to expose the neck of the diverticulum and the papilla of Vater. A probe was inserted down the common duct but it did not enter the diverticulum. The neck of the diverticulum was cut off and closed in two layers, and

FIG. 1. Case 1. Perivaterian duodenal diverticulum demonstrated on cholangiogram. The appearance and position are typical, with the neck of the sac opening by the ampulla of Vater. This fifty-seven year old woman had had cholecystectomy in 1946, but right upper quadrant pain continued. Following removal of the demonstrated diverticulum, the patient has been free of symptoms.

the duodenum was closed. A catheter was left in the common duct down into the duodenum. The patient had a smooth postoperative course. She accidentally removed her tube two weeks postoperatively but in the following eighteen months reported no recurrence of pain.

CASE 11. J. L., a seventy-one year old woman, had had a cholecystectomy in April, 1953, for attacks of biliary colic dating from 1944. Stones were found in the gallbladder at operation. It was known at this time that the patient had a duodenal diverticulum but it was thought wise not to remove it in view of the obvious disease in the gallbladder. Following this procedure, she had several attacks of acute upper abdominal pain quite similar to her preoperative distress. These were associated with tenderness in the right upper quadrant. It was noted that the pain had seemed to be worse after large meals. Jaundice developed two days before her next hospital entry on April 26, 1953. The icterus index was 25 units on May 4, 1953. Two days later the patient was reoperated upon. The common duct was found to be of normal size. The duodenum was turned medially, exposing the diverticulum lying in the pancreas. This was dissected out, and the papilla of Vater was located in

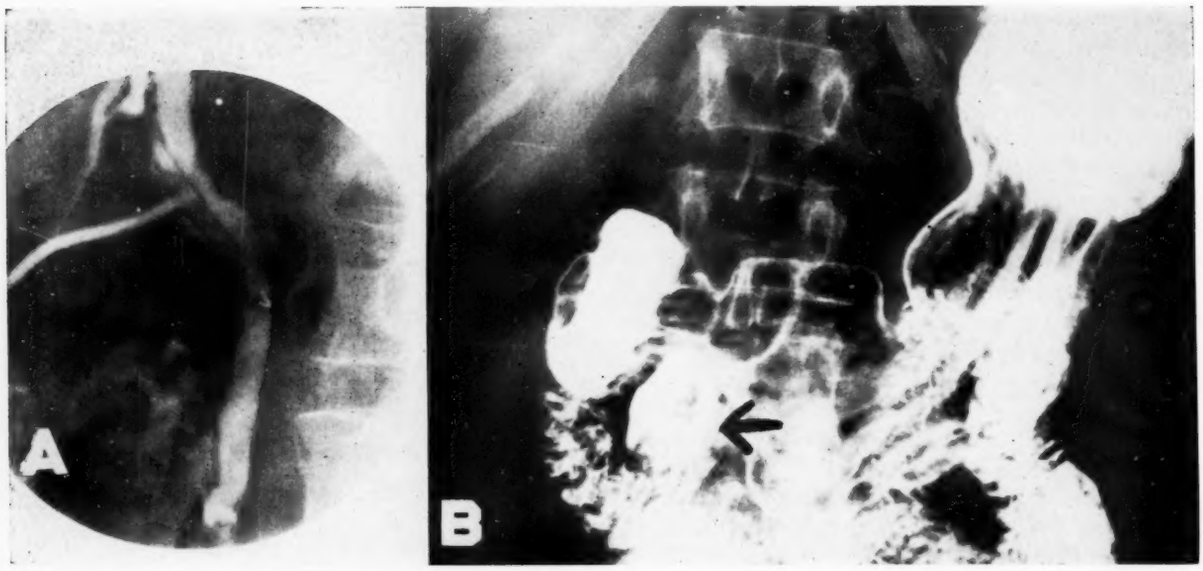

FIG. 2. Case II. A, this seventy-one year old woman had a known perivaterian duodenal diverticulum since 1950. Following cholecystectomy in April, 1953, for cholelithiasis, jaundice developed. On reoperation, no stones were found in the common duct. The duodenal diverticulum was removed and the jaundice cleared. B, barium meal study in April, 1954, revealed another diverticulum not found at surgery in 1953. The patient is asymptomatic.

FIG. 3. Case III. Large diverticulum of duodenum with the neck of the sac anterior to the ampulla of Vater. This patient was a seventy-one year old woman in whom painless jaundice developed in August, 1955. X-ray examination revealed a large duodenal diverticulum. The gallbladder failed to opacify. At surgery, mild pancreatitis was found. Following removal of the diverticulum, the jaundice cleared and the patient is asymptomatic.

the sac close to its neck. The sac was removed and the neck closed, using great care not to damage the papilla. A T-tube was inserted in the common duct. Cholangiograms on June 12, 1953, demonstrated a normal duct system (Fig. 2A), and on July 2nd the tube was removed. An upper gastrointestinal series was done in April, 1954, which again showed a diverticulum in this area, but the patient no longer complained of pain. (Fig. 2B.) This patient has been seen subsequently, the last time being October, 1955; she has had no further trouble.

CASE III. I. R., a seventy-one year old woman had been hospitalized in August, 1955, for malaise, chills and mild jaundice which had gradually deepened over a course of three or four days until her entry. It was known that the patient had hypertension, for which she had been given thorazine,® 10 mg. twice a day, by another physician for some months. She had had no abdominal pain, nausea or vomiting. The gallbladder was palpable; the urine was positive for bile and negative for urobilinogen. Cephalin fluocculation test was normal; the total bilirubin was 7.6 mg. per cent. A gastrointestinal x-ray series showed a duodenal diverticulum (Fig. 3); the gallbladder could not be seen.

Operation two weeks later revealed that the liver was large and of a greenish hue; the gallbladder was thin-walled and contained no stones. The common duct, which did not appear grossly enlarged, was opened. No stones were found and a probe passed easily into the duodenum, which was then opened. The mouth of the 3 cm. diverticulum was found just anterior to the common duct entrance. The opening was enlarged slightly so that the papilla, with a catheter coming through it, could be seen. There was some induration of the head of the pancreas. The sac was removed and its opening was closed with a layer of No. 0000 chromic catgut and one of No. 0000 cotton. A T-tube was placed in the common duct. A biopsy

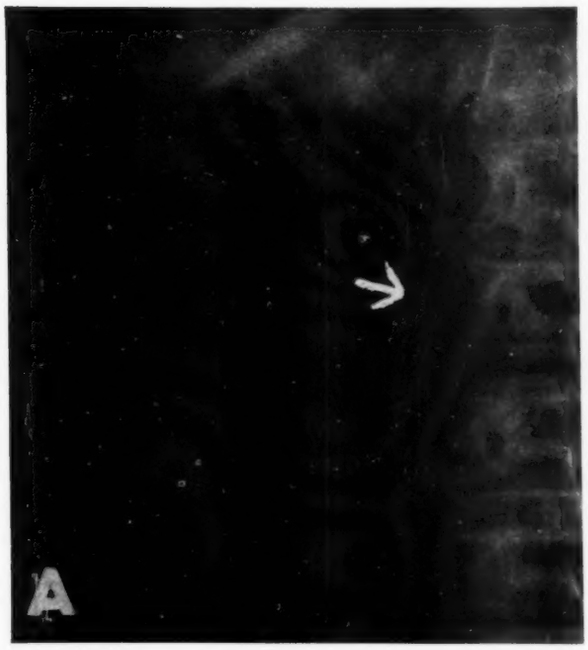

FIG. 4A. Case IV. Following cholecystectomy performed thirty years previously, this sixty-six year old woman complained of right upper quadrant pain, nausea and occasional episodes of vomiting. Intravenous cholangiogram was normal in June, 1955.

FIG. 4B. Same case. Large perivaterian duodenal diverticulum was seen on the upper gastrointestinal series done at the same time. At surgery on July 21, 1955, the orifice of the diverticulum was adjacent to the entrance of the common duct. The patient has been symptom-free since the surgical removal of the diverticulum.

specimen of the liver revealed pigment in the central cells of the lobules and surrounding the central veins; the biopsy specimen of the pancreas showed only mild chronic pancreatitis.

This patient has done well postoperatively, and has had no further upper abdominal symptoms. No further jaundice has been noted, and except for marked fatigue the patient has been quite well.

CASE IV. H. T., a sixty-six year old woman, was seen with the complaint of attacks of nausea, pain and belching, relieved by vomiting. These symptoms had persisted for thirty years. About thirty years previously her gallbladder had been removed. A duodenal diverticulum had been seen on x-ray examination some years before (1950). In the recent past there had been more attacks of nausea and pain, and x-rays three months prior to operation had again demonstrated the diverticulum. (Fig. 4B.) It did not empty well when filled with barium. Intravenous cholangiography demonstrated a common duct which appeared to be normal. (Fig. 4A.)

At operation on July 21, 1955, the duodenum was turned medially and a diverticulum found, its orifice adjacent to the entrance of the common duct into the duodenum. The duct was not opened since it was normal in size and appearance. The diverticulum was removed and its neck closed.

The patient had a smooth postoperative course and has obtained a good result to date. It is interesting that this patient had been called a hypochondriac and operation had been delayed for this reason.

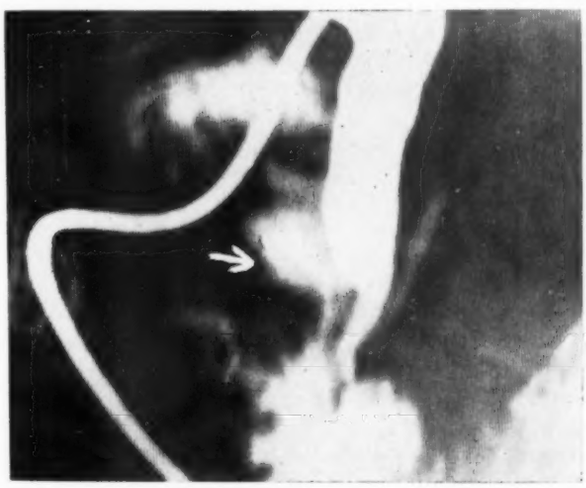

FIG. 5. Case V. A sixty-four year old woman had a cholecystectomy in October, 1954, for acute cholecystitis and cholelithiasis. A biopsy specimen of the pancreas at that time showed subacute pancreatitis. A cholangiogram on December 22, 1954, revealed the duodenal diverticulum which was not seen at surgery.

CASE V. M. H., a sixty-four year old woman, was seen October, 1954, suffering from an acute attack of cholecystitis. At operation the gallbladder

FIG. 6A. Case VI. A thirty-five year old woman with recurrent right upper quadrant pain. In September, 1954, a normal cholecystogram was demonstrated.

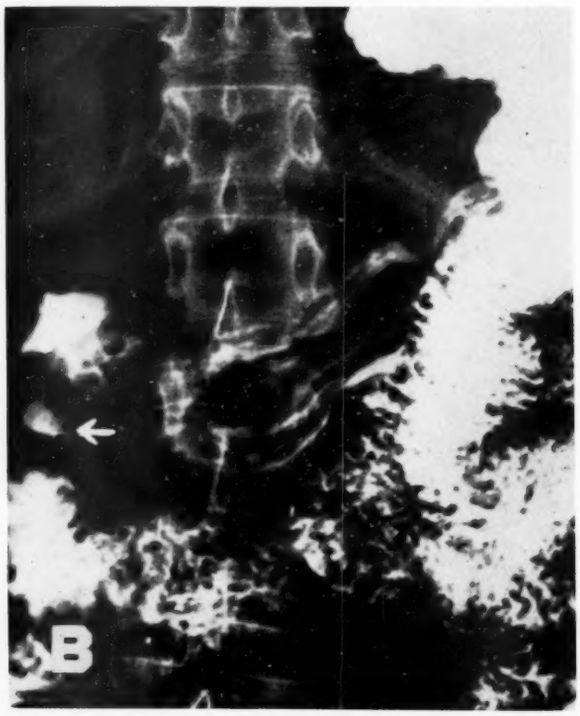

FIG. 6B. Same case. An upper gastrointestinal series in September, 1954, revealed a perivaterian duodenal diverticulum. Since its removal the patient has been free of pain in the right upper quadrant.

was found to be thick-walled and contained multiple stones. The common duct was not enlarged and no stones were palpated in it, nor found on exploration. The head of the pancreas was somewhat indurated. The gallbladder was removed, the common duct was opened and explored, and no stones were found in it. A T-tube was placed in the common duct. Two months later a cholangiogram was made which demonstrated a diverticulum. (Fig. 5.) The T-tube was removed two months later and at six months the patient was having no discomfort. It should be noted that the diverticulum was not seen at operation but a biopsy specimen of the pancreas showed subacute pancreatitis, and a biopsy specimen of the liver revealed bile stasis.

We believe this case demonstrated the effect of the diverticulum on the pancreatic duct, the compression caused by it producing pancreatitis. To date she has had no further symptoms. However, if she has further trouble, we will recommend removal of this diverticulum.

CASE VI. E. C., a thirty-five year old woman, had been seen at intervals for two years with the complaint of right upper quadrant pain, fairly severe at times and worse after large meals, giving the clinical impression of chronic cholecystitis. In September, 1954, an upper gastrointestinal series showed a diverticulum of the descending duodenum. The radiologist thought the opening of the ampulla was near the neck of the diverticulum. (Fig. 6B.) A gallbladder series showed a normal concentration of dye and no calculi. (Fig. 6A.)

At operation on October 27, 1954, the gallbladder was found to be of average size with no stones or adhesions. The liver showed only a slight increase in fibrosis. The retroduodenal space was opened just below the point where the common duct entered the duodenum, exposing the diverticulum which was about 2 cm. in diameter. It was removed and the neck closed with No. 000 chromic and interrupted cotton sutures. The gallbladder was not removed. After a postoperative bout of right upper quadrant pain, attributed to slight leakage at the suture line, the patient has been free of her previous pain.

OPERATIVE PROCEDURE

The operative treatment of duodenal diverticulum may be very difficult, both because of the difficulty in locating the diverticulum and the difficulties of its removal. Since the diverticulum is usually collapsed at the time of opera-

tion, identification may be made much easier by the procedure suggested by Mahorner,[10] namely, the inflation of the duodenum by means of a 22 gauge needle which is inserted through the wall and used for the injection of between 30 and 40 cc. of air to balloon the duodenum and with it the sac of the diverticulum. There may well be more than one diverticulum; the method is also valuable to demonstrate this fact, particularly when only one has been seen by x-ray. The location of diverticula also contributes to the difficulty of exposure, since lying on the medial side of the duodenal loop as they often do, the common duct may not only course along the wall of the sac but also actually enter into it. The sac may be almost entirely intrapancreatic, which makes the exposure, as well as the removal, a good deal more difficult.

The first step in the attack on the diverticulum should be the incision of the peritoneum to the right of the duodenum, rotating the duodenum and retroduodenal portion of the common duct anteriorly and to the left, thus exposing the posteromedial aspect of the duodenal loop. It is here that the diverticulum, which may be interfering with the drainage of the common duct or pancreatic duct, will usually be found. The sac should then be carefully dissected out. The best method of removal is to cut about halfway across the neck close to the duodenum. This allows one to inspect the inside of the neck and locate the ampulla, if it is close to the neck as it frequently is. The mucosa is then sutured with No. 0000 chromic catgut, thus preventing retraction. After the opening has been closed halfway across, the rest of the sac is removed and the suture continued. An outer layer of interrupted nonabsorbable sutures is used to close the muscular layer. If there is any doubt as to the exact relationship of the common duct or of its opening adjacent to or into the diverticulum, the common duct should be opened and a probe or catheter passed down into the duodenum so that it may be positively identified and protected. This will also enable one to close the opening without compromising the diameter of the common duct. It has been suggested by Mahorner and Kisner[10] and others that in difficult cases or when the common duct opens into the diverticulum, inversion of the sac might be the safest and easiest procedure. However, this has disadvantages both in distorting the common duct and in producing local irritation and inflammation. We have not found this procedure necessary in any of our patients.

COMMENTS

We agree that the majority of duodenal diverticula do not produce symptoms. From our experience with the cases cited herein and those reported in the literature, there is no doubt that in certain instances they may cause obstructive phenomena in the biliary and pancreatic ducts. This may be due to distention of the sac with food or due to inflammation of the neck of the sac or of the papilla.

In the series of six cases presented herein, one patient (Case I) was found to have a duodenal diverticulum by cholangiogram after two previous operations on the biliary tract had failed to relieve her pain; she was cured by diverticulectomy. In one other patient (Case II), cholecystectomy was followed by pain and jaundice. This was relieved by removal of a duodenal diverticulum. In another patient (Case IV), nausea and vomiting, the presenting symptoms after cholecystectomy, were similarly relieved by diverticulectomy. In one patient (Case III), jaundice was associated with a duodenal diverticulum in the abscence of gallbladder or common duct stones, but with microscopic evidence of pancreatitis and bile duct stasis. The administration of thorazine beclouds the picture slightly here, but the appearance of jaundice after several months of therapy would make it less likely due to thorazine. In one patient (Case VI) the symptoms suggested cholecystitis, but a normal gallbladder and duct system were found, and removal of the diverticulum gave relief. In Case V bile stasis and pancreatitis were attributed to the duodenal diverticulum, but in view of the presence of acute cholecystitis, there is some doubt whether this has been definitely proved.

Thus, we see that in patients who have had cholecystectomy with return of symptoms or in patients who have symptoms of cholecystitis and common duct obstruction when no stone or stricture is found, one of the causes to be considered and looked for is a diverticulum of the duodenum. Certainly not all patients with post-cholecystectomy syndrome will be found to have such a cause nor would we advise that all duodenal diverticula be removed; but when there is a duodenal diverticulum in the peri-

vaterian area with symptoms of discomfort, pain or both, in the right upper quadrant, not accounted for by stone or stricture in the biliary tract, removal of the diverticulum will offer the patient a reasonable hope for relief.

CONCLUSIONS

1. Diverticula of the duodenum are not uncommon.

2. Those located near the ampulla of Vater or lying along the common duct not infrequently give symptoms of and may be associated with actual biliary tract or pancreatic disease.

3. We believe that the diverticulum should be removed in patients showing such symptoms in this region.

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DISCUSSION

William Brock (Stockton, Calif.): I enjoyed this presentation very much, although I cannot agree that convincing evidence is presented in all cases.

If we are to recognize the autopsy studies of Ackerman and the common radiologic discovery of duodenal diverticula, this anatomic variation is exceedingly common. The reported incidence runs as high as 22 per cent. In the past we have attributed the symptomatology to other upper abdominal lesions, and probably correctly so, although the authors have so ably pointed out the possible effects of these diverticula on the terminations of the common bile and pancreatic ducts. In these cases certainly a surgical attack is the procedure of choice. It has been my experience, however, that so frequently after a complete investigation in the patient with presumably functional symptoms, the only positive finding is the roentgen demonstration of a duodenal diverticulum; or it may be found associated with demonstraable biliary tract or gastroduodenal disease. These are very commonly perivaterian in position. It is here that careful clinical judgment must be exerted in selecting those patients for surgical excision. Technically, the removal of sacs imbedded in the pancreas may be difficult and lead to undesirable results.

I would certainly agree with the authors that, if at all possible, surgical excision rather than inversion is the procedure of choice.

Blake C. Wilbur (closing): The literature describes many cases which have been allowed to progress to a worse state so that the resultant condition was much more obvious. Ogilvie reported on four autopsied cases in which the diverticula, in his opinion, caused pancreatitis and cholangitis, and eventually death. There are quite a few other cases in our experience which are not as clear-cut. However, in three of those we described, one can fairly definitely say there was cause and effect.

Blood and Plasma Volume Studies in Patients with Acute Surgical Lesions of the Abdomen

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MANY studies of the blood volume have been carried out in chronically ill and depleted patients with various abdominal lesions of long duration. However, there have been few investigations of the blood volume in patients suffering from acute surgical lesions within the abdomen. This is surprising because shock not infrequently accompanies various acute intra-abdominal conditions such as peritonitis, perforated ulcer, intestinal obstruction and acute pancreatitis.[1] The present study was undertaken to determine if any changes in blood volume occurred in patients with acute conditions of the abdomen.

MATERIALS AND METHODS

This series consisted of sixty-one patients who were admitted to the Los Angeles County Hospital between 1953 and 1955. All were diagnosed as having acute intra-abdominal lesions, and the diagnosis was verified in fifty-seven patients at surgery. In the remaining four patients with acute pancreatitis (corroborated by appropriate laboratory studies), surgery was not performed. In this group of sixty-one patients the following conditions were present: perforated peptic ulcers, twenty-three; perforated afferent loop of a gastrojejunostomy, one; perforated abdominal esophagus, one; small bowel obstruction, twelve; infarction of the small bowel, two; paralytic ileus, one; acute large bowel obstruction, four; traumatic wounds of the abdomen, four; acute intra-abdominal infections, five (three acute appendicitis, two acute cholecystitis); acute pancreatitis, four; acute pyloric obstruction, two; acute obstruction of the cardia of the stomach, one; and intra-abdominal bleeding following cholecystectomy, one. The ranges in plasma and blood volume are shown in Table I, along with the hematocrit values.

The blood and plasma volumes were determined by means of a modified Evans blue dye method.[2] The hematocrit was ascertained by the use of the Wintrobe tube. Since this was the peripheral venous hematocrit, a hematocrit correction factor of 0.915 was used.[3] The total blood volume measurements were based on the body hematocrit rather than on the peripheral venous hematocrit. The plasma and total blood volumes were related to the surface area rather than to body weight alone. The expected plasma volumes were also based on the surface area (height-weight formula of DuBois, 1936): area in $cm.^2$ = wt. kg. $0.425 \times$ ht. cm. $0.725 \times K$ (71.84). The standard deviation in the expected plasma volume of the male was found to be $\pm 1/6$ of the volume, while in the female it was $\pm 1/8$ of the volume. The expected total blood volumes were calculated from the expected plasma volumes and the highest level of normal body hematocrit values. This was found to be 42.5 in a series of normal persons.[4] The standard deviation in the blood volume of the male was found to be $\pm 1/7$ of the volume, while in the female the standard deviation was $\pm 1/13$ of the volume. The blood volume determinations were carried out in most of these patients before any fluids had been administered. The standard error of the method employed here was 1.65 per cent.

TABLE I

Types of Cases	No. of Cases	Plasma Volume		Blood Volume			
		Maximum		Maximum Decrease	Corrected Hematocrit	Maximum Increase	Corrected Hematocrit
		Decrease	Increase				
Perforations, upper alimentary tract	25	− 934	+1497	−1007	26.9	+2928	31.29
Obstructions of alimentary tract	22	−1047	+ 113	−1278	34.0	+1990	65.0
Intra-abdominal infections	5	− 296	+ 632	− 825	44.2	+1551	47.6
Intra-abdominal trauma	4	− 752	+ 183	− 927	40.8	− 5	36.13
Pancreatitis	4	−1973	+ 123	−2549	52.7	+ 390	44.7
Intra-abdominal bleeding	1	−2370	.....	−3859	42.8	.....	.....

STATISTICAL ANALYSIS

Of the twenty-three patients with perforated peptic ulcer, eleven had normal plasma and blood volumes coming within the standard deviation of the expected normal value; three exhibited elevated plasma and blood volumes, and three showed reduced plasma and blood volumes; two had decreased blood volume with normal plasma volume; two had elevated blood volume with normal plasma volume; one each had an elevated and decreased plasma volume with normal blood volume. In the one patient with perforation of the afferent loop of a gastrojejunostomy and the patient with the perforation of the abdominal esophagus, the plasma volume and the total blood volume were normal. (Table II.)

TABLE II
UPPER GASTROINTESTINAL TRACT PERFORATIONS
(TWENTY-FIVE CASES)

	Plasma Volume Increase	Plasma Volume Normal	Plasma Volume Decrease
Blood volume increase	3	2	0
Blood volume normal	1	13(2*)	1
Blood volume decrease	0	2	3†(1*)

* Intravenous fluids given prior to plasma volume determinations.

† The only female in this group of twenty-five cases is included in this total.

Of twelve patients with small bowel obstruction, the plasma volume was increased in one, normal in seven, and reduced in four. (Table III.) The total blood volume was increased in three, normal in eight, and decreased in one. Four of these patients had received parenteral therapy prior to volumetric measurements. Of the two patients with infarction of the small bowel, the plasma volume was significantly reduced in one, and the blood volume significantly reduced in the other. The single patient with paralytic ileus had a significant reduction of only the blood volume. Only one of the four patients with large bowel obstruction showed a significant reduction of the

TABLE III
GASTROINTESTINAL TRACT OBSTRUCTIONS
(TWENTY-TWO CASES)*

	Plasma Volume Increase	Plasma Volume Normal	Plasma Volume Decrease
Blood volume increase	1† (male)	1† (female)	1 (male)
Blood volume normal	0	9 (5†) (6 males, 3 females)	5 (2 males, 3 females)
Blood volume decrease	0	2 (1 male, 1 female)	3 (2 males, 1 female)

* Includes: stomach, two; duodenum, one; small bowel, fifteen; colon, four.

† Intravenous fluids given prior to plasma volume determinations.

plasma and blood volume. In all four an acute obstruction was superimposed upon a carcinomatous obstruction of the large bowel. The single patient with carcinomatous obstruction of the cardia had normal plasma and blood volumes. In one patient with ulcerous obstruction of the pylorous, the plasma volume was reduced; and in the patient with carcinomatous obstruction of the pylorus, the plasma and total blood volumes were normal.

TABLE IV
MISCELLANEOUS CASES*

	Plasma Volume Increase	Plasma Volume Normal	Plasma Volume Decrease
Blood volume increase...	1 (female)	3 (1 female, 2 males)	0
Blood volume normal....	0	5 (1†) (all males)	1 (male)
Blood volume decrease...	0	1 (male)	3 (1†) (all males)

* Includes: traumatic injuries, four; inflammatory lesions, five; pancreatitis, four; postoperative bleeding cystic artery, one.
† Intravenous fluids given prior to plasma volume determinations.

Of the four patients with acute pancreatitis, three exhibited normal plasma and blood volumes, while one showed a reduction of both. (Table IV.) Of the three patients with acute appendicitis, two had significant increases and one a significant decrease in blood volume, while their plasma volumes were within normal range. The two patients with acute cholecystitis exhibited an elevation of the blood volume; one had an elevated plasma volume, and one a normal plasma volume. Of the four patients with acute traumatic injuries to the abdomen, the plasma volume was significantly reduced twice and the blood volume once, the remaining results falling within the range of normal. In the single patient with postoperative intra-abdominal bleeding following cholecystectomy both the plasma and blood volumes were significantly decreased.

Thirteen patients with perforation of the upper alimentary tract exhibited plasma volume reductions, four of which exceeded 500 cc. (Fig. 1.) In eleven patients there was an apparent increase; in four this exceeded 500 cc. In those with significant increases in plasma volume, the duration of the disease was twelve hours or less; and in those exhibiting significant decreases, the disease had been present more than twelve hours. This is illustrated by the course of the mean curve.

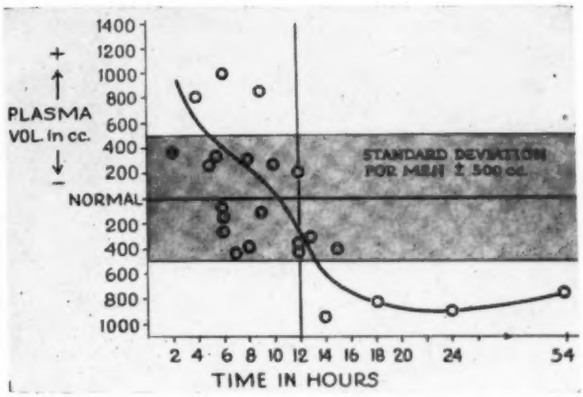

FIG. 1. Upper alimentary tract perforations (twenty-five cases).

The amount of intraperitoneal spill was measured in thirteen patients with perforated duodenal ulcer. (Fig. 2.) All with elevated plasma volume had measured spills of less than 500 cc., while those with decreased plasma volume had spills in excess of 500 cc., the maximum measuring 1,750 cc.

In the untreated group of obstructions the plasma volumes fell within the zone of lower normal or just below. (Fig. 3.) About 50 per cent of the values were within the normal range, and the remainder were significantly reduced. The values in the treated cases were either normal or elevated. Because the number of cases was small, too much importance cannot be attached to the behavior of the plasma and blood volume curves. For the first nine days of illness, the two curves are not significantly different. Beyond this time there is a tendency for the blood volume to decrease. In this group it is significant that the plasma and blood volume curves are so nearly similar.

Of the four patients with acute pancreatitis, the plasma volume was reduced to the extent of 350 cc. in one, and 2,000 cc. in a second. In two patients, insignificant increases (180 to 200 cc.) were present in the blood or plasma volumes, or both. In the four patients with acute traumatic injuries to the abdomen, the volume reductions ranged up to 1,200 cc. One patient had a lowered blood pressure (88/70) and an insignificantly reduced plasma volume of 300 cc. In the patient with intra-abdominal bleeding following cholecystectomy, shock was present (blood pressure, 70/60; pulse rate, 160).

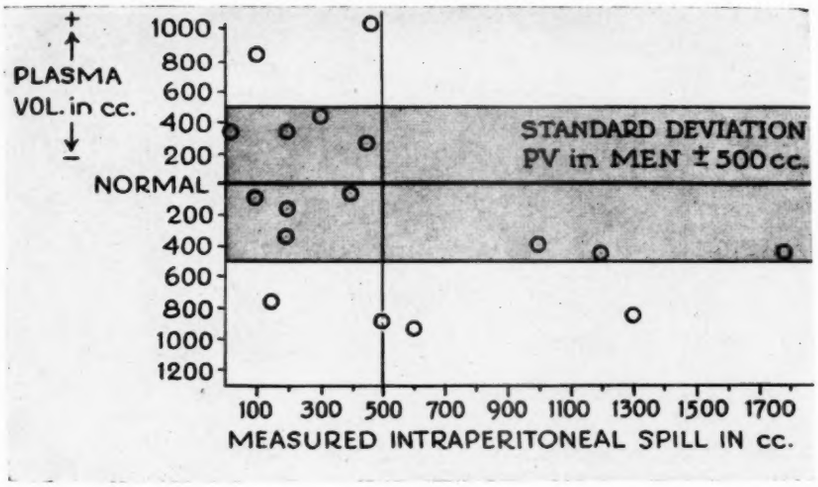

FIG. 2. Perforated peptic ulcer. Alterations in plasma volume related to measured intraperitoneal spill.

The plasma volume was found to be reduced by 2,300 cc., and the blood volume by 4,000 cc.

Of the three patients with acute appendicitis, the single patient with a perforated appendix and free pus in the peritoneum showed considerable reductions in both the plasma and blood values (600 cc. and 1,000 cc., respectively).

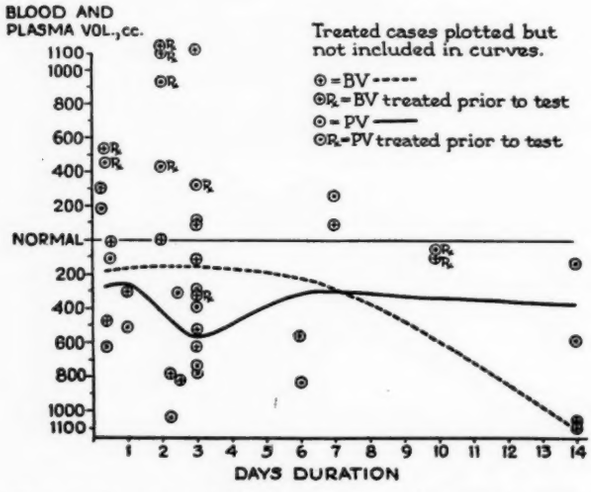

FIG. 3. Plasma and blood volume of obstructed group.

The disease had lasted six days before this patient was hospitalized.

COMMENTS

Before discussing the theoretic and practical aspects of the clinical studies described herein, it may be pertinent to review the major points of controversy concerning blood volume determination by the dye dilution method. The first of these is the validity of the dye method. Limitations of space preclude an elaborate discussion of this point; for such a discussion the reader is referred to the review by Reeve.[5] The overwhelming body of evidence obtained during recent years indicates that the simultaneous use of Evans' blue dye (T-1824) and of other tagged albumin methods, such as radioactive iodinated human serum albumin (R 1 HSA), give estimates of the plasma volume which are, for all intents and purposes, identical. The methods employing red blood cells tagged with radioactive isotopes (such as P-32) give somewhat smaller blood volume measurements than do the tagged albumin methods. However, it is not at all conclusive that such tagged red cell methods are necessarily more accurate than are the tagged albumin methods such as that in which the Evans blue dye is employed.

A second controversial point is the "cat" effect. This consists of a rapid removal of the Evans blue dye by the reticuloendothelial system before the dye has had sufficient time to become firmly united with the circulating serum albumin. It was so named because it was observed in cats in which part of the injected Evans blue dye is phagocytosized by the reticuloendothelial system.[6] This gives erroneously high plasma volume readings. However, in dogs and human beings, the rate of disappearance of the injected dye seems to be related to the rate of turnover of serum albumin in the liver. Attempts to reproduce the "cat" effect in dogs and in human beings

have not met with success.[7,8] Although Mather and his co-workers[9] have observed it occasionally in human beings, these other workers are not in agreement with Mather and his group. Plentl and Gelfand[10] could find no evidence of the existence of the "cat" effect in human beings.

A third controversial point concerns the standard of reference of the volume measurements. Should they be related to weight, height, surface area or lean body weight? This problem is discussed in some detail by Davis.[1] There are great variations in the plasma volume even in persons of comparable age, sex, height and weight. Mather and his associates[9] were unable to find any correlation between the plasma volume and the height, weight or body surface. Nevertheless, it is the consensus that expected volumes based on body weight alone are more likely to be erroneous than are those based on the surface area. For this reason, the plasma volumes in the method employed herein[2] have been related to the surface area. In a recent study of methods of predicting plasma volume, Inkley and his co-workers[11] concluded that both the Evans blue dye and the I-131 serum albumin tagged methods gave comparable values. They found that the correlation of the plasma volume to the lean body mass had a standard deviation of 317 cc.; the correlation of the plasma volume to the total body weight had a standard deviation of 273 cc.; the correlation of the plasma volume to the surface area had a standard deviation of 267 cc. These data suggest that to relate the volume measurements to the surface area may give more predictable values.

What is the reason for the increased blood and plasma volumes present in many of the patients in this series? It was at first suspected by us that this did not represent a true increase in these values. Such apparent "increases" were noted particularly in some of the patients with perforated peptic ulcers, acute cholecystitis and acute appendicitis. In all of these, a focus of intraperitoneal irritation was present. It was pointed out by Wiggers[12] that escape of Evans' blue dye might occur in patients with peritonitis. We suspected that the "increases" were due to loss of dye-tagged albumin through injured capillaries in the peritoneum. This hypothesis was subjected to investigation. Fluid from the peritoneal cavity of three patients with perforated ulcer was analyzed for Evans' blue dye after acetone extraction. In these patients the blood volume had been determined by the dye method several hours earlier. Small amounts of dye were found in the peritoneal fluid, but not in sufficient quantities to explain the hypervolemia in some of

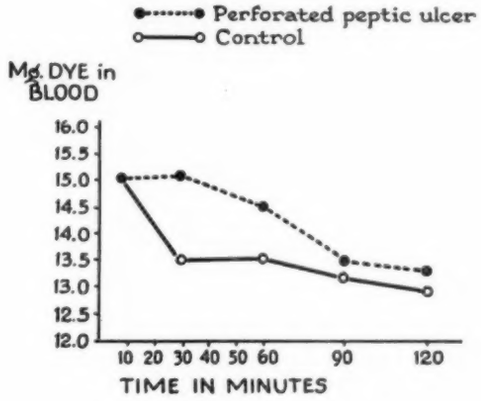

FIG. 4. Dye reduction curves.

these patients. The rate of disappearance of the injected Evans blue dye was determined at intervals up to two hours in three control patients and in two patients with perforated peptic ulcer. (Fig. 4.) It was demonstrated that the rate of disappearance of the dye from the blood was not significantly different in the two groups; in fact, the rate of initial disappearance of dye was more rapid in the control group. This would suggest that the increase in plasma and blood volumes may be real rather than apparent; however, further study of this problem is needed and contemplated. It is suggested that this hypervolemic reaction may represent one type of response of the organism to severe stress. These increases are more often seen in early cases of perforated peptic ulcer (up to twelve hours) than in those observed after twelve hours.

What is the relation of the blood and plasma volume reductions to the blood pressure? It is generally agreed that there is some correlation between the extent of reduction of the blood volume and the degree of fall in blood pressure. The reader is referred to a discussion of this point.[1] There is, however, a better correlation between the lowering of the cardiac output reduction and the decrease in blood volume.[13] Only seven in this group of sixty-one patients had a systolic blood pressure of 90 mm. Hg or less at the time the blood and plasma volumes were determined. These are listed in Table v.

It is evident that the amount of blood volume reduction or plasma volume reduction, or both, is not well correlated with the extent of reduction of blood pressure. This poor correlation was most evident with lesser reductions of the volume values. When the reduction was great, the blood pressure tended to be lowered.

TABLE V
RELATIONSHIP OF REDUCED BLOOD PRESSURE TO PLASMA VOLUME AND BLOOD VOLUME

Patient*	Condition	Alterations		
		Blood Pressure	Pressure Volume	Blood Volume
P. R.	Perforated gastric ulcer (12 hr.)	60/40	− 416	− 530
C. C.	Perforated duodenal ulcer (14 hr.)	90/70	− 934	− 920
W. H.	Perforated gastrojejunal ulcer (6 hr.)	70/50	− 82	−1,007
C. G.	Laceration abdominal wall (1–2 hr.)	88/70	+ 2	− 48
A. R.	Postoperative cholecystectomy bleeding (8 hr.)	70/60	−2,370	−3,859
E. M.	Acute pancreatitis (14 hr.)	90/75	−1,973	−2,549
S. B.	Incarcerated femoral hernia (3 days)	90/?	− 741	− 624

* All the patients listed are male.

In order to determine the effects of age and duration of the disease upon the volume measurement, the single largest group of patients, namely, those with perforation of the alimentary tube, was studied. Seven patients were sixty years of age and older in this group of twenty-five. In three of the seven, the duration exceeded twelve hours. All showed reduced plasma volumes. In the remaining four, the plasma value was increased in one, significantly decreased in one, and unchanged in the remaining two.

Of those patients under sixty years of age with symptoms less than twelve hours, three showed reduced blood volume (plasma volume) and nine showed increased plasma volume. In the group under sixty, but with symptoms of more than twelve hours' duration, the plasma volume decreased in five, and one came within the normal standard deviation. This suggests that the factor of duration is more important than that of age in influencing plasma and blood volume changes.

The results of the studies described herein suggest that blood volume determinations should be carried out in patients with acute surgical conditions of the abdomen, particularly if these are of a duration exceeding twelve hours. It is in this group that blood volume reductions or plasma volume reductions, or both, are most likely to be observed. If such determinations are not available, our results suggest that the administration of blood transfusions should be considered in patients in whom the acute surgical condition within the abdomen has lasted twelve hours or longer.

SUMMARY AND CONCLUSIONS

Studies of the plasma and blood volumes by the Evans blue dye method have been carried out in sixty-one patients with acute surgical conditions of the abdomen. Reductions of the blood volume of considerable degree are noted in many of these patients. Apparent "increases" in the blood volume or plasma volume, or both, have been noted in a number of patients with an intraperitoneal form of irritation. Our studies fail to suggest that these "increases" may be due to escape of the dye into the peritoneal fluid through abnormally permeable capillaries, but rather to a true hypervolemia, an increase in plasma volume and/or blood volume, or both. This may represent one type of response of the organism to stress. The precautions to be made in determining the blood volume are discussed. Patients with acute surgical lesions of the abdomen of more than twelve hours' duration often have a reduction of the plasma volume or blood volume, or both, of sufficient degree to warrant blood transfusion.

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DISCUSSION

Frederic P. Shidler (Menlo Park, Calif.): Drs. Joergenson, Davis and Woolley have measured the blood volumes in sixty-one patients with acute abdominal lesions. Their numerous data are difficult to assimilate because they were obtained in specific acute disease and extrapolated into broad disease categories although the age of the disease at the time of blood volume measurement was a variable.

A reduced blood volume is of clinical significance when its consequences may produce oliguria, brain ischemia or deep vein thromboses. In the acute abdominal diseases studied, diminished blood volumes nearly always are attributable to hemorrhage, extracellular fluid losses either from the vascular or the interstitial fluid compartments, or rarely to the collection of blood in the splanchnic pool in response to pain or blood-borne chemical stimuli.

Acute abdominal disease will not produce diminished blood volume unless it produces a loss of blood or plasma. The data in this series corroborate this clinical observation, for in all cases of duodenal ulcer perforation in which the surgeon found more than 500 cc. of fluid in the peritoneal cavity, there was measurable blood volume loss. On the other hand, few of the patients with bowel obstruction showed diminished plasma volume loss, and none of them apparently had peritonitis or large amounts of fluid within intestinal loops.

The large number of normal plasma volume values in the entire series probably means there was little or no uncompensated plasma loss from the circulation of these patients. An examination of the clinical management of these patients might show they required no specific blood volume replacement in their therapy.

I am not qualified to discuss critically the method used by the authors in measuring blood volume. It seems to be similar to methods usually used. I do not think the results obtained are laboratory errors, but rather accurately represent blood volume in the patients under study. I do not think we can measure to exact figures the fluid shifts from one extracellular compartment to another. Such shifts result from hydrostatic, osmotic and ionic forces both within the vascular and the interstitial fluid compartments, but measurable only in the former.

We can only conclude that the astute clinician, augmented by certain laboratory tests, can best estimate an ill patient's circulating blood volume and that blood volume replacement should be determined by clinical judgment.

Charles E. MacMahon (Seattle, Wash.): In commenting on this paper, I would like to give you some of our own unfortunate experiences in our efforts to determine accurately the blood volume variations in the surgical patient. I am certain that the basic physiologic concepts emphasized by Dr. Zollinger at Ohio State and Dr. Lyons at Tulane are valid. We have had errors similar to Dr. Joergenson's, which like his, have been in the direction of hypervolemia. The error in blood volume determinations in this direction probably is due to the fact that the vascular bed is not a closed system and there may be leaks into the extravascular spaces. A possible area of pooling, disassociated from the vascular tree, might well be in the liver bed, as suggested in an earlier paper given on refrigeration experiments. We have been using, rather than Evans' blue, a technic of blood volume determinations utilizing radioactive iodine latched onto a serum albumin molecule. Despite the seemingly foolproof technic and with the aid of our physicist, we have occasionally had hypervolemic errors of such magnitude that it would suggest that the patient's blood weight was in excess of the body weight. When quantitative errors in this direction and of this magnitude occur, it is obvious that we will still have to rely on clinical judgment in effecting adequate blood replacements.

Harry A. Davis (closing): I think it is generally recognized that there is no absolutely accurate

method of determining the blood or plasma volumes. In general, these methods can be divided into two groups: (1) those which employ plasma diluents such as Evans' blue dye or radioactive iodinated serum albumin; and (2) those in which tagged red blood cells (tagged, for example, with radioactive phosphorus) are used. The radioactive iodinated albumin and the Evans blue dye methods, in general, give comparable results. The plasma diluent methods yield blood volume values which are slightly higher than those obtained by the tagged red cell methods.

My concluding remarks will be directed toward emphasizing those points which Dr. Joergenson has made, namely, that while the great majority of patients with acute surgical abdominal conditions have no significant changes in the blood or plasma volumes, an appreciable number of such patients do show significant reductions. We believe such reductions should be looked for, particularly if the patient's illness has lasted for longer than twelve hours. It is particularly in this group, we believe, that shock is liable to occur on the operating table or afterward if such hidden volume reductions are not recognized and corrected.

Regarding the hypervolemic response described herein, we cannot say very much. Evidence has been presented which suggests that it is not due to a technical error. If it is not a technical error, then it certainly represents a very unusual type of response of the organism to stress. We do not know the reason for this hypervolemia. Perhaps neurogenic or humoral factors are involved. Further work is needed and is contemplated along this line.

Liver Function Tests in Obstructive Jaundice

REVIEW OF RESULTS IN 100 CASES

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MANY biochemical tests have been devised for the assessment of hepatic function.[1] The value of some of these tests is established with regard to the differential diagnosis and management of patients with hepatic disease.[2,3] Most writers have emphasized the role of the function tests in the study of patients with hepatocellular or medical jaundice. The surgeon, however, is concerned chiefly with hepatic disturbances secondary to extrahepatic obstruction to bile outflow. Under these circumstances somewhat lesser degrees of hepatic cellular impairment results and often dysfunction is not indicated by the tests. How then, should the surgeon use the liver function tests, what do they mean, what are their limitations and when does the effort, time and expense (Table 1) which they entail justify their application?

The liver is the great and everchanging chemical factory of the body. It has been estimated that more than 500 reactions occur within the liver, and for the study of these reactions some 100 tests have been described in the last ten years alone.[4] Many hepatic function tests are complicated or cumbersome, others provide no meaningful information, and still others are so variable and inconclusive that in themselves they often confuse rather than aid the physician.[5] It is apparent that no single test or series of tests can be expected to measure precisely the host of activities in which the liver participates, yet there are definite areas in which well chosen and carefully interpreted tests can provide information helpful to the clinician.

The principal reasons which make testing of various liver functions difficult are: (1) The tremendous reserve capacity of the liver. This fact is illustrated by the observation that experimentally about 80 per cent of the liver can be removed without producing serious metabolic disturbances. (2) The great regenerative power of the liver. Again in the experimental animal removal of about 80 per cent of the liver is followed with nearly complete regeneration within a few weeks. (3) Dissociation of functions. At any one time, one or more hepatic functions may be impaired while others are normal. Thus certain hepatic functions are altered without respect to other functions, and also, the separate functions change with time.

TABLE 1

COST OF LIVER FUNCTION STUDIES AT UNIVERSITY HOSPITALS (AS OF FEBRUARY 1, 1955)

Serum bilirubin	$3.75
Alkaline phosphatase	4.75
Cephalin flocculation	3.25
Thymol turbidity	3.25
Zinc sulfate flocculation	3.25
Cholesterol, total	3.25
Cholesterol esters	3.25
Plasma protein and albumin-globulin ratio	4.75
Prothrombin	4.00
Bromsulfalein	3.25
Total	$36.75

TESTS FOR LIVER FUNCTION

What are the functions of the liver which we usually attempt to measure? They may be grouped into two broad categories: (1) excretory and (2) metabolic. It must be granted that such a division is both incomplete and oversimplified but it is adequate for purposes of this discussion.

The excretory function of the liver can be measured by the level of the serum bilirubin. In the presence of hepatic parenchymal damage and extrahepatic bile duct obstruction, the serum bilirubin often rises and jaundice ap-

pears. There has been much discussion about the determination of serum bilirubin fractions (direct and indirect) or the van den Bergh test in the differential diagnosis of jaundice. In our experience we have found these determinations generally to be uninformative and therefore unnecessary.

Studies of the level of excretion of the products of pigment metabolism in the urine and feces are of great practical value in the recognition of the several types of jaundice. Although quantitative estimation of the levels of excretion of these substances is sometimes required, it has not been our practice to order these tests routinely in jaundiced patients. More often simple observations and qualitative tests for urobilinogen and bilirubin in the urine and feces have proved satisfactory. This is not to be construed to mean that the quantitative tests need never be used.

The enzyme (or several enzymes) alkaline phosphatase, which is a product of osteoblastic activity, is excreted by the liver through mechanisms somewhat different from those which transfer bilirubin. Thus in obstructive jaundice the levels of serum alkaline phosphatase and the serum bilirubin do not always parallel each other. Levels of serum alkaline phosphatase above 15 Bodansky units encountered in jaundiced patients who do not have abnormal osteoblastic activity (e.g., fractures, tumors of bone, etc.) are usually associated with extrahepatic obstruction.

Bromsulfalein retention is an excellent test of the excretory function of the liver but the test is usually reserved for non-jaundiced patients. Excretion of bromsulfalein is similar to that of bilirubin. Because jaundice *per se* indicates impairment of the excretory function, the test is of no special value in jaundiced patients.

There are several tests which are designed to assess the metabolic functions of the liver. Generally, carbohydrate metabolism remains relatively unaltered except under conditions of extreme disease of the liver. For this reason, this facet of liver metabolism is not measured routinely. To some degree, fat metabolism may be assessed by estimating the levels of the serum cholesterol and cholesterol esters. Although cholesterol and cholesterol ester levels have been determined in many of our cases, we have found them to be subject to so much variation and difficulty in interpretation that they are rarely helpful. Further discussion of carbohydrate and fat metabolism of the liver as measured by function tests will therefore be omitted.

Lowering of the total serum proteins and reversal of the values of albumin and globulin are often associated with serious liver disease. The liver is the site of albumin, fibrinogen and prothrombin synthesis. Under conditions of hepatic dysfunction the ability to fabricate these substances is impaired. The globulins are produced by the cells of the reticuloendothelial system, of which the liver next to the bone marrow is the most important member. A rise in the serum globulin is often associated with inflammation in any area of the body. In diffuse hepatic disease a fall in albumin fraction indicates impaired anabolism of protein and a rise in globulin fraction represents a response to inflammation. These findings always suggest a serious disturbance in metabolic balance and the surgeon must recognize the need for vigorous measures to correct the deficiency and to restore more nearly optimum levels of hepatic function as soon as possible. It should be emphasized that protein deficiencies are usually apparent to the seasoned practitioner and that the laboratory determination of the serum protein level will generally only confirm his clinical impression.

The flocculation tests (cephalin flocculation, thymol turbidity and zinc sulfate flocculation) are not strictly tests of liver function. Instead, they reflect certain aberrations in serum proteins which often occur in hepatic diseases. These tests are empiric, non-specific, incompletely understood and frequently unpredictable. They are generally negative in uncomplicated obstructive jaundice and positive when hepatic cells are undergoing autolysis (e.g., in toxic and viral hepatitis). When obstructive jaundice is complicated by hepatic infection, fatty infiltration, neoplastic replacement, passive congestion, etc., one or more of the flocculation tests are likely to be positive. When all flocculation tests are positive, the implication must be that severe hepatic damage exists.

The precise deviations in the circulating proteins which the flocculation tests indicate are unknown but all have to do with changes in the globulins. The cephalin flocculation test is the most sensitive and perhaps the most widely used. The thymol turbidity test is sim-

ple and practical for everyday use. Zinc sulfate flocculation is also a useful test but it is probably less specific for hepatic disease.

We have not used the colloidal gold flocculation test or the mucoprotein test for assessing liver function on our service.

The prothrombin test is used for the detection and treatment of hemorrhagic tendencies of jaundice. Lowered prothrombin levels have not commonly been encountered in our patients surveyed with the one-stage Quick prothrombin estimation. On our service, patients with obstructive jaundice are given vitamin K preparations routinely during the preoperative period, and only when a lowered prothrombin level is observed initially is serial testing performed until the desired elevation of prothrombin is achieved. No instances of postoperative hemorrhage ascribable to an inadequate prothrombin level have been observed in this series. The prothrombin response test as such has not been used to measure hepatic function.

Indications for Liver Function Tests. The battery of liver function tests may be said to play a limited role in the investigation and management of most cases of obstructive jaundice. More important to successful treatment are a complete and thoughtful clinical history, careful physical examination, simple tests of pigment excretion in the urine and feces, and a few days of observation in the hospital. In occasional cases a battery of more complicated tests and serial observations are necessary; in a small group of patients, perhaps not more than 5 per cent, a definite diagnosis can be established only at operation. Although needle biopsy of the liver and peritoneoscopy have many advocates, we have preferred exploratory operation for patients with jaundice of obscure origin.

Liver function tests are helpful under the following circumstances:[7] (1) to assist in the differentiation of the type of jaundice; (2) to aid in the management of the patient (i.e., to detect and measure various types of hepatic insufficiency, to follow the trend of the disease, to aid evaluation of the surgical risk, to aid in the selection and timing of the operation and to estimate residual damage after recovery).

Patients who present themselves shortly after the onset of jaundice (from a few days to two or three weeks) due to probable extrahepatic obstruction and who are in good general health are subjected to the following hepatic function tests: total serum bilirubin, urine urobilinogen and bilirubin (qualitative) fecal urobilinogen (qualitative), serum alkaline phosphatase, thymol turbidity and plasma prothrombin.

During preoperative preparation the tests need not be repeated unless they are abnormal on the initial examination or other clinical data indicate their need. If the patient responds satisfactorily to treatment, a second battery of tests is not secured. The color of the stool and urine, and quantitative tests of pigment excretion are performed and recorded by medical students assigned to the wards.

TABLE II
CAUSES OF OBSTRUCTIVE JAUNDICE

Condition	No. of Cases
Stones in common bile duct	34
Carcinoma of pancreas	27
Subacute cholecystitis	12
Carcinoma of bile duct and gallbladder	9
Chronic pancreatitis	4
Stricture of common duct	2
Miscellaneous	12

If the patient gives a history of long-standing and/or intense jaundice and is obviously quite ill, a more extensive study of hepatic function is instituted. In addition to the foregoing the survey may include any or all of the following tests: cephalin flocculation, zinc sulfate turbidity, total serum proteins and albumin-globulin ratio, and serum cholesterol and cholesterol esters.

Under these circumstances serial tests may be indicated during the pre- and postoperative periods. The patient's response to treatment is again a most important index of recovery, and frequently the liver function tests provide little additional information. There is, however, a correlation between improvement or deterioration in the patient's general condition and the status of liver function as indicated by carefully chosen serial tests.

Findings in Patients with Extrahepatic Jaundice. We have studied 100 consecutive cases of surgical jaundice (Table II) with respect to the clinical findings, liver function tests and pathologic changes encountered at operation or autopsy. In most instances the patients were

TABLE III

POSITIVE LIVER FUNCTION TESTS IN OBSTRUCTIVE JAUNDICE

Diagnosis	No. of Cases	Alkaline Phosphatase (Above 15 Bodansky Units)	Flocculation (One or More Tests)	Prothrombin (Decreased)	Serum Proteins (Decreased or Ratio Reversed)
Subacute cholecystitis	12	18%	55%	18%	0
Stones in common duct	34	22%	33%	15%	16%
Carcinoma of pancreas	27	68%	48%	17%	4%

seen by at least one of the authors. During the course of the study we have attempted to anticipate the degree of hepatic damage as indicated by aberrations in liver function tests and to correlate the clinical and biochemical findings. We have found no close correlation except at the extremes, that is, those patients with early and uncomplicated obstructive jaundice often have no evidence of hepatic impairment, and those patients with severe or prolonged jaundice and clinical evidence of hepatic insufficiency usually have moderate to severe alteration of the liver profile. This is in keeping with the concept that obstruction to bile outflow produces progressive hepatic damage.

The liver biopsy material has also been reviewed in an attempt to correlate histopathologic alterations with the results of the liver function tests. These studies have also revealed a lack of correlation except in the very early and the very late cases. It appears to us that only a limited prediction of existing hepatic disease can be made on the basis of the hepatic function tests. This is consistent with the findings of others who have found no close relationship between the appearance of the liver cell and the function of the cell as indicated by the several tests.[8]

We have attempted to analyze our data statistically but have found that so many variables are involved that such an analysis would be meaningless. There is, however, a trend in the results of the tests which appears to be conditioned by the nature of the agent producing obstruction of the duct; the degree and duration of obstruction, the presence or absence of infection of the hepatobiliary tract, the association of malnutrition and pre-existent hepatic damage, and the patient's response to treatment.

When this series was segregated according to etiologic diagnoses, the cases appeared to fall into categories, each exhibiting a slightly different degree of impairment of the excretory and metabolic functions of the liver. Thus cases of mild jaundice and partial obstruction of the common duct due to subacute cholecystitis and cholelithiasis were placed at one end of the scale, and those cases of severe or complete and sustained obstruction of the bile duct due to cancer of the head of the pancreas were placed at the other end. Cases of jaundice due to stone, stricture, compression from chronic pancreatitis and infiltrative cancer of the gallbladder and bile ducts would be expected to fall somewhere in between.

This separation, according to diagnoses, pointed up a notable trend toward progressive increase in the severity of impairment of hepatic function, particularly in three categories. (Table III.) It appeared that patients with jaundice due to subacute cholecystitis commonly exhibit slightly elevated serum bilirubin levels, normal serum alkaline phosphatase levels and variable flocculation tests. Patients with jaundice due to common duct stones often have higher serum bilirubin levels, elevated serum alkaline phosphatase levels and flocculation tests which are normal or slightly positive. Patients with complete obstruction of the bile duct (and often obstruction of the pancreatic duct) due to cancer of the head of the pancreas generally exhibit highest serum bilirubin and serum alkaline phosphatase values, with one or more positive flocculation tests.

Function tests in obstructive jaundice due to conditions other than those listed heretofore appear to fall between the findings noted for obstruction of the common duct and cancer of the pancreas. The total number of patients which we have collected in other categories is small and the marked variation which exists from case to case and category to category,

however, makes it impossible to draw further conclusions.

CONCLUSIONS

From the review of this material the following generalizations are proposed regarding the assessment of hepatic function by means of liver function tests in the patient with obstructive jaundice:

1. Other things being equal, the intensity of the jaundice as measured by the serum bilirubin determination is an indication of the severity of the obstructive process and the degree of hepatic damage. The need for preoperative treatment directed toward the restoration and maintenance of liver function and early relief of obstruction, by operation if indicated, is apparent.

2. Elevation of the serum alkaline phosphatase in jaundice provides corroborative diagnostic evidence of obstruction to bile flow. The test is also of some prognostic value when determined serially. Beyond this we do not regard the test as particularly helpful.

3. Decreased levels of serum proteins, especially when associated with a decrease in the albumin and a rise or relative rise in the globulin fraction, indicate serious impairment of hepatic function. Surgical intervention under these circumstances is attended with a high degree of risk. Efforts should be made to restore the circulating proteins prior to undertaking operative procedures.

4. Hepatic flocculation tests are quite unpredictable, and except in patients who are seriously ill the tests are as likely to be negative as positive. Sometimes one or more of the tests give positive results, while the results of other tests remain negative. Such aberrations are difficult to explain; but when results of all flocculation tests become positive, one must assume that severe liver damage exists.

5. When the prothrombin concentration is decreased, the risk of hemorrhage is increased. Usually in extrahepatic jaundice a prompt rise in prothrombin occurs in response to administration of vitamin K. If a satisfactory response does not occur, the implication is that hepatic function is impaired. Thus the diagnosis is established *ex juvantibus* or by observing the response to treatment, a valuable but often neglected method of clinical diagnosis.

6. The clinical examination is the most important facet in the diagnosis and management of the patient with obstructive jaundice. The hepatic function tests serve only a limited purpose and are helpful only when the clinical and biochemical data are correlated and integrated into the over-all picture. In general, there appears to be a relationship between the severity and duration of the pathologic process causing the jaundice and the results of the tests of liver function. A complete battery of liver function tests is unnecessary when the clinical examination indicates extrahepatic obstruction and the patient is in good general health.

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DISCUSSION

C. S. Stone, Jr. (Seattle, Wash.): Drs. Gius and Jurayj have given us a very complete review of the value of the various liver function tests in the diagnosis and management of patients with jaundice due to extrahepatic biliary tract disease. I shall not attempt to discuss all the tests that they have so fully commented upon, but will limit my remarks entirely to the alkaline phosphatase test.

Our experience has demonstrated the alkaline phosphatase to be of particular value when it dissociates from the bilirubin, that is, when it is normal in a jaundiced patient or when it is elevated in a non-jaundiced patient. For example, when the bilirubin is elevated, a normal phosphatase is very strong evidence against an extrahepatic cause for the jaundice. Elevation of both bilirubin and phosphatase, however, can occur with either surgical jaundice or parenchymal liver disease.

On the other hand, when the bilirubin is normal but the phosphatase is elevated, we have come to expect one of two general types of disorder: (1) either an intrahepatic, space-occupying lesion such as metastasis, hepatoma or abscess, or (2) a partial,

low grade, incomplete obstruction of the biliary tract such as a small stone in the common duct, a calculus in one of the hepatic radicals or an early-developing stricture.

It is generally known that metastases to the liver can elevate the phosphatase without causing jaundice, but it is less widely appreciated that low grade obstruction from gravel or a small stone in the common duct or hepatic radicals can also bring about elevation of the phosphatase.

There is as yet no satisfactory explanation for this phenomenon. Dr. A. B. Gutman has shown experimentally that a rise in phosphatase without jaundice may follow ligation of one of the small tributaries to the biliary tree. Although no completely satisfactory explanation exists for the elevation of the phosphatase, the validity of the test is not compromised.

We have been particularly interested in the alkaline phosphatase test at the Mason Clinic for the past two and a half years. During this period over 2,000 patients suspected of or known to have hepatobiliary dysfunction have been subjected to this test. Dr. T. Gibbons has correlated the phosphatase level with other liver function tests, the clinical picture and the pathologic findings, and will shortly publish his observations.

This study shows the alkaline phosphatase to be particularly useful under the following circumstances: (1) before gallbladder surgery on the non-jaundiced patient as a clue to the presence of ductal stones which would require exploration of the common duct; (2) before surgery for cancer, regardless of the site but especially with gastrointestinal lesions, to predict the presence of hepatic metastases; (3) in patients with diagnostic problems including those with lung shadows, gastric lesions and suspected pancreatic lesions; and (4) postoperatively in the evaluation of postcholecystectomy symptoms and in the follow-up study for prognostic purposes of patients previously operated upon for malignant disease.

We are entirely in agreement with Dr. Gius that the alkaline phosphatase test is very valuable in surgical jaundice as confirmation if it is elevated, but it is especially helpful in excluding surgical jaundice if the phosphatase is normal. Furthermore, this test has been, in our experience, equally helpful in evaluating the non-jaundiced patient with hepatic or biliary disease.

Siegfried F. Herrmann (Tacoma, Wash.): I have enjoyed this presentation very much because it was a confession of inability to understand all these tests. That has been bothering me for years. I have had that difficulty with internists and with medical men; usually when they ask me to operate upon a patient they think has proved obstructive jaundice, it turns out to be a case of hepatitis.

I wanted to ask Dr. Gius if he has had any aid from needle aspiration of the liver to help distinguish between hepatic disease and obstructive jaundice.

I would like to add, facetiously, my own experience with this test in one case. I think we could call it the Herrmann test to differentiate between obstructive and non-obstructive jaundice. My mother-in-law, who was eighty-five years old, was ill and I was called upon to see her. She had lost her appetite and was somewhat jaundiced. She had been ill for two months. I called in one of our smartest internists and put my mother-in-law in the hospital; the internist and I agreed that she had, probably, infectious hepatitis. Many tests were performed several times and the results were always the same, infectious hepatitis. However, she got no better and I asked my confrere how it would be to put a needle in the liver to see if we could get any help that way. He said, "I wish you would." I performed needle aspiration of the liver and had to jump out of the way, for when I put the needle in, white bile squirted out across the room. After I let the liver drain a while, I pulled the needle out and made a diagnosis of obstructive jaundice. We then subsequently operated upon her and found that she had cancer of the head of the pancreas. I was able to anastomose the common duct to the jejunum and she had a year of relative comfort. Needle aspiration in this case was quite helpful.

John A. Gius (closing): I wish to thank Drs. Stone and Herrmann for their discussions. Dr. Herrmann's new test is an interesting one, but I am not enthusiastic about needle biopsy. I prefer to make an incision and to see what I am doing.

One thing I did not mention was the relative lack of correlation which is found between the histopathologic sections and the liver function tests. This is well established in medical jaundice and we came to the same conclusion with regard to cases of obstructive jaundice in which liver biopsy was done. There is, however, some correlation at the extremes; in early obstructive jaundice liver functions would be normal and changes within the hepatic parenchyma as viewed microscopically, would be minimal. In those cases with late and far advanced jaundice and extensive liver disease the presence of marked changes in the function tests and advanced changes in the histopathologic picture would be noted. In general, however, there is little correlation between the morphology and the physiology of the hepatic cell as assessed by present methods.

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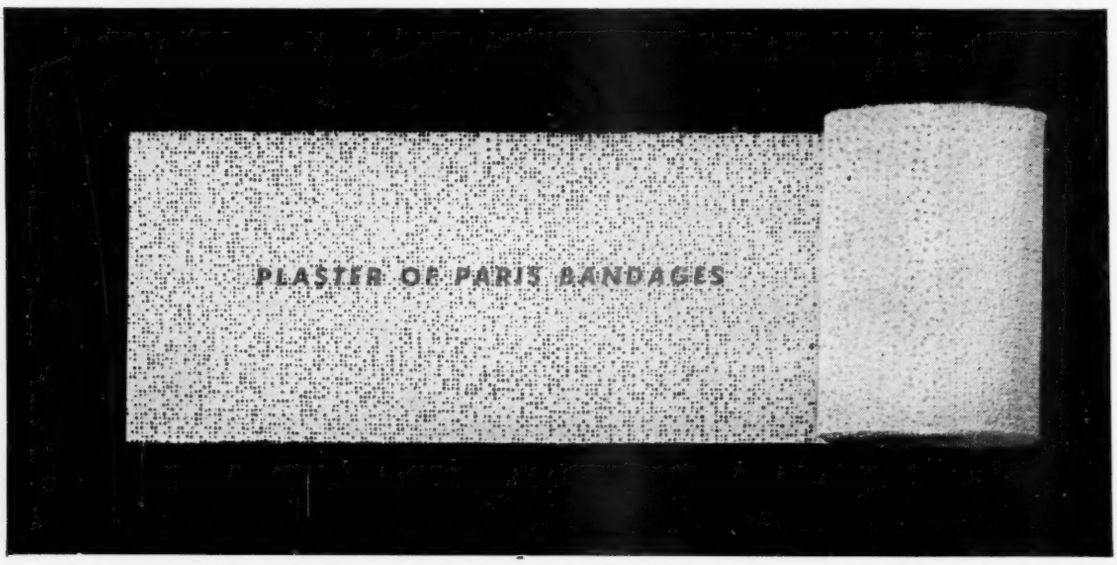

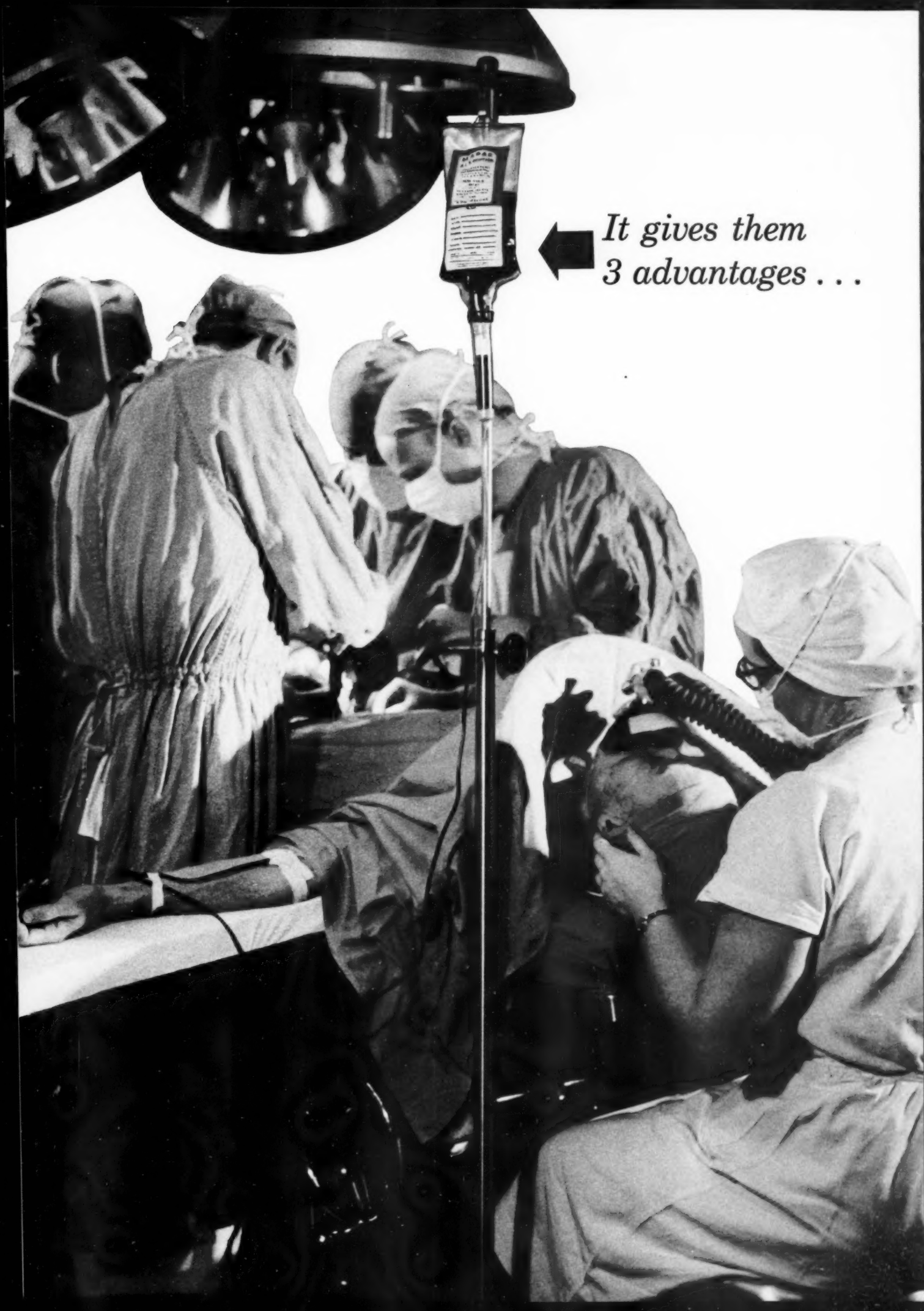
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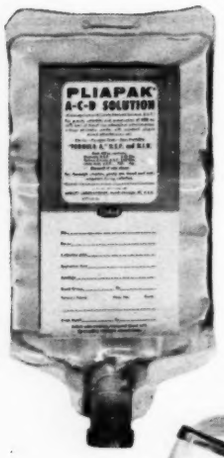

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REFERENCES—1. Muether, R. O., Sommer, A. J., and Koster, B., "Studies on Blood Stored in Plastic Bags," *Am. J. Clin. Path.*, 23:818, Aug., 1953. 2. Knudtson, K. P., "Plastic Blood Containers," ibid., 813

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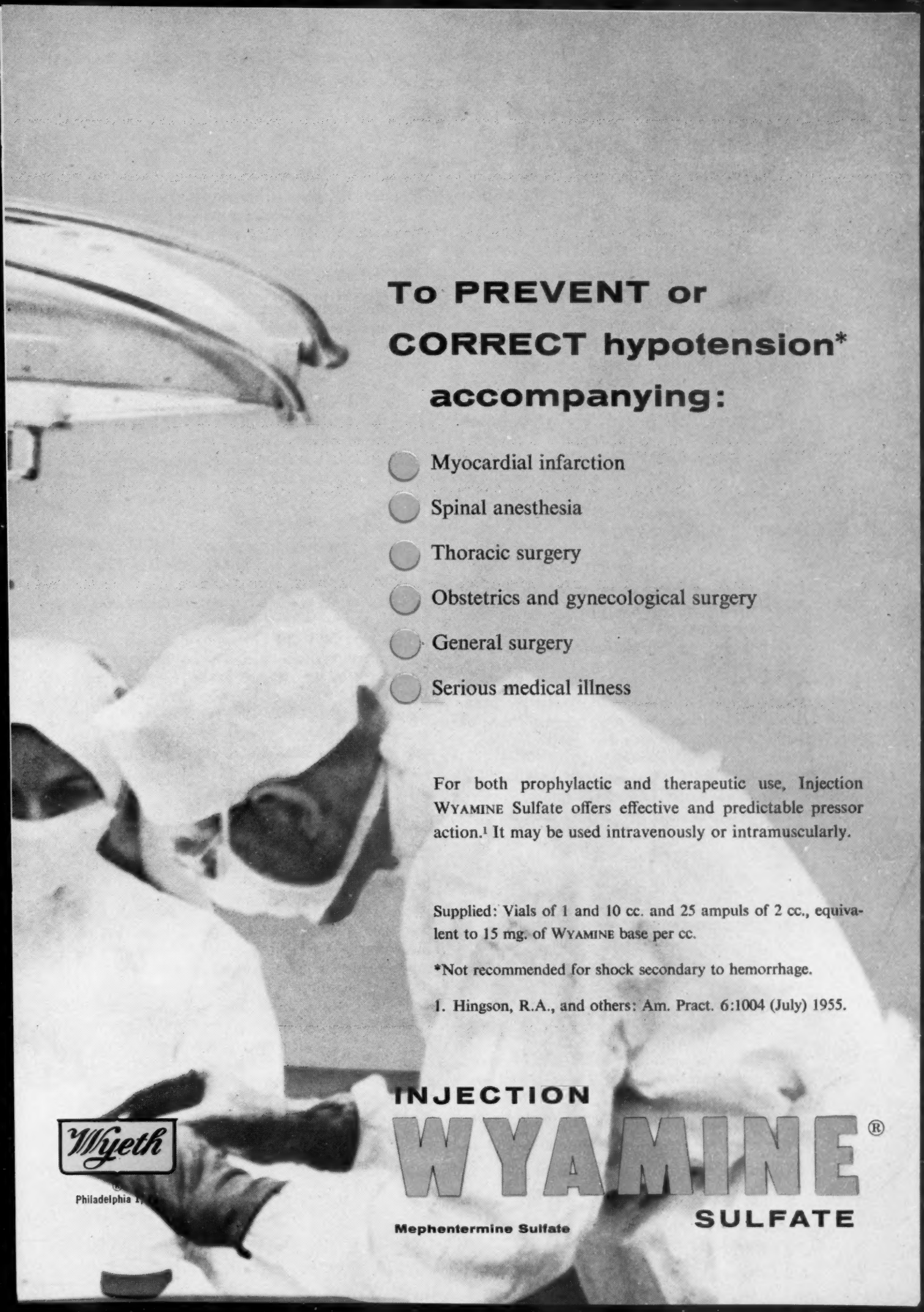

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1. Hingson, R.A., and others: Am. Pract. 6:1004 (July) 1955.

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NOTES AND QUOTES

DR. LOYAL DAVIS, Chairman of the Department of Surgery at the Northwestern University Medical School, was elected President of the American Surgical Association at its recent annual meeting in White Sulphur Springs, W. Va.

An internationally known neurosurgeon, Dr. Davis is an honorary fellow in the Royal College of Surgeons of England, and a regent of the American College of Surgeons. He is editor of the surgical journal, *Surgery, Gynecology and Obstetrics*, and is attending surgeon at the Passavant Memorial Hospital in Chicago.

A graduate of Northwestern University medical school, he has served as a colonel in the U. S. Army medical corps and as consultant on neurologic surgery to the chief surgeon of the European theatre of operations. (Our sincere congratulations—*Ed.*)

Heart attacks now kill as many women as men, suggesting a possible link between heart ills and smoking.

Addressing the American Chemical Society's New York Section, Dr. Stanley W. Hartcroft, Chairman of the Department of Pathology at the Washington University Medical School, St. Louis, said that whereas twice as many men as women died from myocardial infarction (heart attack) between 1910 and 1940, data from 1940 to 1955 indicate that just as many women as men now succumb to this killer. He based his statements on statistical studies just completed by Dr. Wilbur Thomas and Dr. Kyu Lee, also of Washington University.

Today's equality between the sexes in the matter of heart attacks can be attributed to the fact that, in the age group over sixty, more women than men are now victims of this disease, Dr. Hartcroft observed, adding:

"I almost hesitate to suggest it, but perhaps these women over 60 who are now dying more frequently of myocardial infarction than are the men represent a group of our population that started smoking for the first time 20 years ago.

"The men had always smoked to this extent, and therefore we would not expect to see any change in their death rates from myocardial infarction since 1940 as compared to before 1940."

NEEDLE holders with new, improved "bulldog" jaws have been introduced by Edward Weck & Co., Inc. of New York. In this new Weck needle holder, the serrated areas of the jaws have been hardened by a special carburizing process forming complex carbides that provide just the right combination of hardness to resist wear, assure a firm grip, and at the same time, protect the needle from injury. The serrations are an integral part of the jaws, not an insert, and are so patterned that the needle fits snugly into the grooves. The jaw ends of these new needle holders are also finished in the new Weck "glare-proof" finish to eliminate reflections from bright overhead lights in the operating room.

A unique "writing partnership" between two United States medical students netted them two of three top awards and $1,000 cash in an international medical writing contest.

The students have been announced as winners of the 1955 Schering Award, open to all medical students in the United States and Canada. Now in its eleventh year, the contest annually awards three $500 first prizes and $250 second prizes for the best papers submitted on three selected medical topics of current interest.

The successful contestants, Charles King Mervine and David Charles Schechter, who are both attending Jefferson Medical College in Philadelphia, co-authored the two prize-winning papers, topping entries from more than eighty other medical schools. Subjects of their papers were "The Prevention and Treatment of Blood Transfusion Reactions" and "The Management of Osteoporosis."

SMOKING usually does not interfere with the mechanics of breathing in healthy people; it may even help. However, if the smoker has heart or lung disease, the opposite may be true and damage done to the breathing process.

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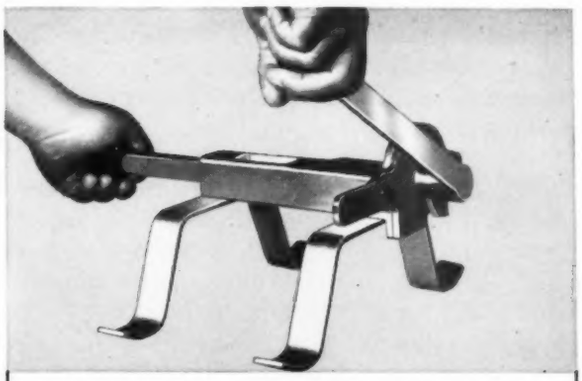

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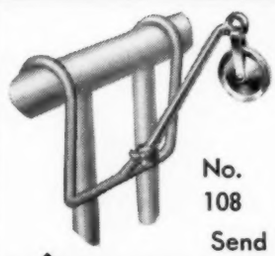

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determined by the mechanics of breathing. The greater the work of breathing, the smaller the amount of work available for non-respiratory work, such as physical activities.

Becton, Dickinson and Company, East Rutherford, N. J., has announced association of its interests with Bard-Parker Company, Inc., of Danbury, Conn., through an exchange of stock on May 1st.

The Bard-Parker firm is well known in the medical profession for its surgeons' blades and holders. Becton, Dickinson and Co. is an important producer of hypodermic equipment, clinical thermometers and elastic bandages.

The plant operations of neither company will be affected by the new association. The consolidation of their resources and technical skills affords greater emphasis on product research and development which will benefit the medical profession and hospitals.

DESPITE increased postponement of widowhood to the older ages as a result of the declining mortality prior to mid-life, last year 115,000 wives were widowed in the United States through the death of a husband less than fifty-five years of age, according to the Metropolitan Life Insurance Company's statisticians.

At the time of the last census there were, in all, 700,000 white widows in the United States who had lost their husbands within the preceding decade, and who were under fifty years old at the time of their loss. Of these, almost one-third had been widowed two to four years, and one-half for five to nine years.

Tornadoes in the United States took 1,766 lives during the decade 1946 through 1955, and inflicted injuries on approximately ten times that many persons according to the Metropolitan Life Insurance Company's statisticians.

During the ten-year period the loss of life varied considerably from year to year. Over the past forty years, however, there has been a general tendency for the fatality toll to decrease from one decade to the next—the 1916 to 1925 toll being 3,114, the 1926 to 1935 figure 2,138, and the 1936 to 1945 figure 1,896.

May was the peak month for tornadoes during the past decade, accounting for nearly one-fourth of the deaths. Fatal injuries from this cause are also quite frequent in other months of the spring and early summer.

VIOLENT deaths take the lives of more nurses than do communicable diseases. This unexpected revelation, indicating a shift in occupational hazards, came to light in a ten-year follow-up of student nurses conducted by the U. S. Public Health Service. The study, which embraced 26,000 nurses and covered the years 1943 to 1953, was directed at finding out how much clinical tuberculosis developed among nurses in general hospitals and how many died of the disease. It was under the direction of Dr. Carroll E. Palmer, Director of the Tuberculosis Program, Division of Special Health Services, P. H. S., Washington, D. C.

Andrew Theodore of P. H. S., who presented the report, stated that ninety-six of the former student nurses had died when the follow-up was considered completed in 1954, only about half as many as might have been expected to die if mortality rates for white women of comparable age in the general population had prevailed.

Among the ninety-six deaths, thirty-five were from violent causes—accidents, suicides and homicides. Motor vehicle accidents accounted for the largest number of violent deaths, taking fourteen lives. Overdoses of barbiturates accounted for seven, suicides for six, monoxide poisoning for two, and murder, one. Mr. Theodore pointed out that possibly the barbiturate and monoxide deaths were also suicides.

Seemingly miraculous recoveries from athletic injuries just are not so, a Duke University physician declared recently.

Apparent miracles come about in relatively minor injuries and are due to early adequate treatment, Dr. Lenox D. Baker, Duke orthopedic surgeon, declared. Dr. Baker has served as trainer and physician for athletic teams for more than thirty years.

"The concern of the partisan public in the well-being of their favorite athlete frequently has resulted in over-emphasis and over-publicity of the occurrence and the seriousness of athletic injuries," he said.

"The tendency of an occasional coach or

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publicity man to use the so-called 'crying towel' or 'bleeding heart' technique has exaggerated not only the degree of the injury but the importance of its recipient," he added.

"When such a player makes an apparently phenomenal recovery and leads his team to victory, interest is then centered in the magic treatment or perhaps on the possible abuse to which he has been subjected." It is easy to understand the speed and degree of recovery when the seriousness of the injury has been exaggerated, he said.

"Pathologically, injuries to athletes are no different from injuries to other individuals," he emphasized. For several reasons, however, the athlete often stands a better chance of recovery.

"The principles of treating injuries in athletics are the same as the principles of treating injuries in the industrial field, the home accident case or the traffic victim, but there is no insurance or compensation involved—no fears of loss of security. There is that more important factor of all which percentagewise cannot be evaluated—desire. All the injured athlete wants to know is 'Can I play Saturday?'"

NORTHWESTERN UNIVERSITY has announced a group hospitalization program for its 8,000 students on the Evanston and Chicago campuses. The plan, approved recently by the Board of Trustees, will be effective next fall. The program will be integrated with the existing student health service and will contain the following features: (1) hospital coverage anywhere in the world; (2) benefits of $17 per hospital day and $250 toward diagnostic procedures up to a maximum of $1,000 per illness; (3) a surgical fee schedule up to $300; (4) an increase of campus infirmary care from five to fourteen days per quarter; (5) discontinuation of special fees for x-ray and laboratory work within the student health service; (6) an option permitting coverage to continue during summer vacations; and (7) an option to permit coverage of a spouse and children.

Dr. Leona B. Yeager, Director of Student Health Service, stated that special consideration was given to providing a type of health coverage that directly benefits commuter as well as resident students. She said another principal consideration was to protect students against "disaster" situations when serious injury or prolonged illness can consume funds intended for educational purposes and cause permanent withdrawal from school.

The Seventh Congress of the Pan-Pacific Surgical Association will be held in Honolulu, Hawaii November 14–22, 1957. All members of the profession are cordially invited to attend and are urged to make arrangements as soon as possible if they wish to be assured of adequate facilities. An outstanding scientific program by leading surgeons with sessions in all divisions of surgery and related fields promises to be of interest to all doctors. Further information and brochures may be obtained by writing to Dr. F. J. Pinkerton, Director General of the Pan-Pacific Surgical Association, Young Bldg., Honolulu, Hawaii.

AT least some anticancer drugs fail to cure cancer in humans because a few of the cancer cells are too versatile—if they cannot make vital chemicals one way they do it another way.

These preliminary results of research at the University of Wisconsin were announced recently by the American Cancer Society which supports the work by Dr. Gerald A. LePage of the McArdle Institute. Drs. J. F. Fernandes and Anton Lindner collaborated in some of the work. The study is significant in view of the increasing likelihood that anticancer drug treatment will follow the pattern of antibiotic treatment for infectious disease. Just as there are many kinds of antibiotics for many kinds of infection, so are there an increasing number of compounds for many types of cancer.

Almost all the drugs commonly used against cancer today block a specific vital chemical reaction within the cell. Because cancer grows and metabolizes faster than normal cells and because cancer is less discriminating than normal cells in the nutrients it takes in, it will take up poisons rejected by normal cells. These poisons destroy a cell's ability to manufacture protein or nucleic acid or some other essential chemical of life.

Scientists have found that some of the drugs will kill all but an extremely small percentage of cancer cells and almost, but not quite, cure the cancer patient. The cells which escape destruction multiply, their offspring form new tumors which are impervious to the drugs, and eventually they kill the patient.

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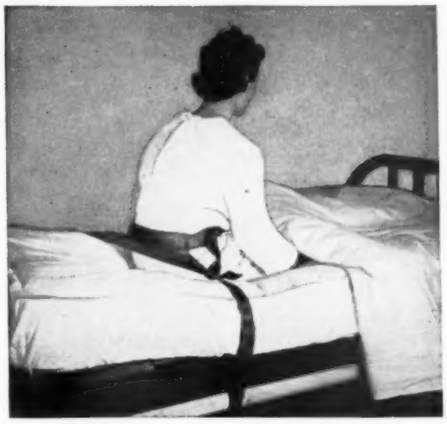

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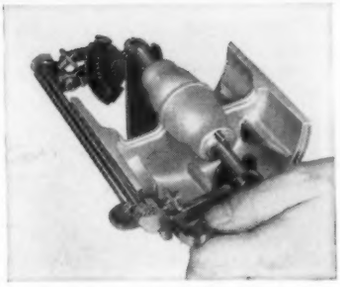

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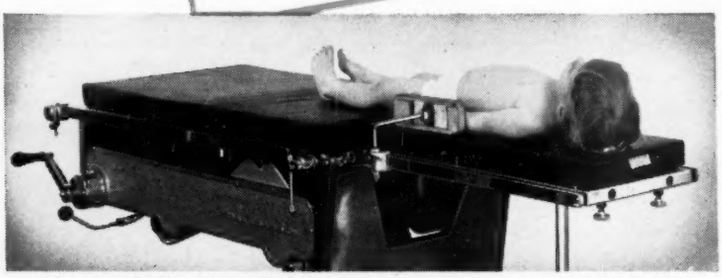

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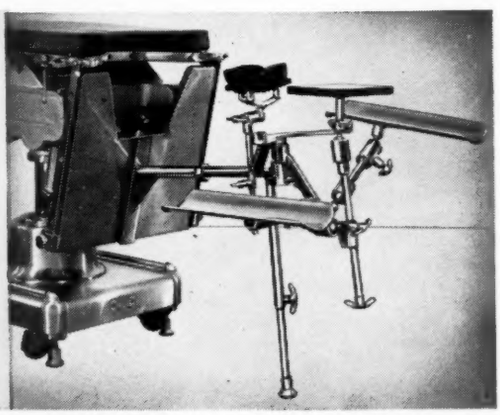

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